

AN OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF OBESITY
EDITED BY ARNE ASTRUP, COPENHAGEN. VOLUME 10, SUPPLEMENT 1, MARCH 2009 ISSN 1467-7881

**Central aspects of sugars
in human nutrition**

obesityreviews

iaso


WILEY-
BLACKWELL

obesityreviews

Volume 10 Supplement 1 March 2009

Central aspects of sugars in human nutrition

Guest Editors

Andreu Palou



**WILEY-
BLACKWELL**

obesity reviews

An Official Journal of the International Association for the Study of Obesity



Editor

Professor Arne Astrup MD PhD
Department of Human Nutrition
Faculty of Life Sciences
University of Copenhagen
Rolighedsvej 30
DK-1958 Frederiksberg C
Denmark

Editorial Assistant

Ms Claude Mona

Production Office

Ms Catherine Ng
obr@oxon.blackwellpublishing.com

Editorial Board

Dr David B. Allison, New York, USA
Dr Maarlen A. van Baak, Maastricht, the Netherlands
Professor Ottavio Bosello, Verona, Italy
Dr Mikael Fogelholm, Helsinki, Finland
Dr Alfredo Halpern, Sao Paulo, Brazil
Dr Susan Jebb, Cambridge, UK
Dr Dominique Langin, Toulouse, France
Dr Yvonne Linné, Huddinge, Sweden
Professor Yuji Matsuzawa, Osaka, Japan
Dr Donna H. Ryan, Baton Rouge, USA
Dr Anne Thorburn, Victoria, Australia
Dr Angelo Tremblay, Québec, Canada

Publisher

Obesity Reviews is published by Blackwell Publishing Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK. (Tel: +44 (0) 1865 776868; Fax: +44 (0) 1865 714591).

Blackwell Publishing is now part of John Wiley & Sons.

Aims and Scope

Obesity Reviews is a review journal publishing papers from all disciplines related to obesity. It should, therefore, appeal to all professionals with an interest in obesity, most particularly to endocrinologists, cardiologists, gastroenterologists, obstetricians but also rheumatologists, as well as health professionals working in general medicine and surgery. Furthermore, the journal will contribute to education and interprofessional developments by planning *pro et con* reviews on current controversies.

Obesity Reviews is an official review journal of the International Association for the Study of Obesity, which has over 7,000 members, in 38 countries, with a rapidly increasing membership status.

A special subscription rate is available for individuals who are members of the national associations under the umbrella of the International Association for the Study of Obesity.

The journal is published on a bimonthly basis. The Editorial policy will be to minimise the period between submission and publication of reviews, while retaining high standards of quality exercised by peer review.

Abstracting and Indexing Services

The Journal is indexed by *Index Medicus* and *Medline*.

Information for subscribers

Obesity Reviews is published in six issues per year. Subscription prices for 2008 are: Premium Institutional: £381 (Europe), US\$703 (The Americas), £419 (Rest of World). Personal: €137 (Europe, Euro zone), £91 (Europe, non-Euro zone), US \$171 (The Americas), £102 (Rest of World). Prices are exclusive of tax. Australian GST, Canadian GST and European VAT will be applied at the appropriate rates. For more information on current tax rates, please go to www.wiley.com, click on Help and follow the link through to Journal subscrip-

tions. The Premium institutional price includes online access to the current and all online back files to January 1st 1997. For other pricing options, including access information and terms and conditions, please visit www.interscience.wiley.com/journals.

Delivery Terms and Legal Title

Prices include delivery of print journals to the recipient's address. Delivery terms are Delivered Duty Unpaid (DDU); the recipient is responsible for paying any import duty or taxes. Legal title passes to the customer on despatch by our distributors.

Journal Customer Services

For ordering information, claims and any enquiry concerning your journal subscription please go to interscience.wiley.com/support or contact your nearest office:

Americas: Email: cs-journals@wiley.com; Tel: +1 781 388 8598 or 1 800 835 6770 (Toll free in the USA & Canada).

Europe, Middle East and Africa: Email: cs-journals@wiley.com; Tel: +44 (0) 1865 778315

Asia Pacific: Email: cs-journals@wiley.com; Tel: +65 6511 8000

Despatch

OBESITY REVIEWS, (ISSN 1467-7881) is published bimonthly in January, March, May, July, September and November. US mailing agent: Mercury Airfreight International Inc., 365 Blair Road, Avenel, NJ 07001, USA.

Periodical postage paid at Rahway, NJ. Postmaster: Send all address changes to OBESITY REVIEWS, Journal Customer Services, John Wiley & Sons Inc., 350 Main St., Malden, MA 02148-5020.

Copyright and Photocopying

Journal compilation © 2008 International Association for the Study of Obesity. All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means without the prior permission in writing from the copyright holder. Authorization to photocopy items for internal and personal use is granted by the copyright holder for libraries and other users registered with their local Reproduction Rights Organisation (RRO), e.g. Copyright

Clearance Center (CCC), 222 Rosewood Drive, Danvers, MA 01923, USA (www.copyright.com), provided the appropriate fee is paid directly to the RRO. This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes, for creating new collective works or for resale. Special requests should be addressed to: jrights@wiley.com

Back issues

Single issues from current and recent volumes are available at the current single issue price from customerservices@blackwellpublishing.com. Earlier issues may be obtained from Periodicals Service Company, 11 Main Street, Germantown, NY 12526, USA. Tel: +1 518 537 4700, Fax: +1 518 537 5899, Email: psc@periodicals.com

Disclaimer

The Publisher, the International Association for the Study of Obesity and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher, the International Association for the Study of Obesity and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, the International Association for the Study of Obesity and Editors of the products advertised.

This journal is available online at Wiley InterScience. Visit www3.interscience.wiley.com to search the articles and register for table of contents e-mail alerts.

Access to this journal is available free online with institutions in the developing world through the HINARI initiative with the WHO. For information visit www.healthinternetwork.org

Imprint details

Printed in Singapore by Markono Print Media Pte Ltd

For submission instructions, subscription and all other information visit: www.blackwellpublishing.com/obr
ISSN 1467-7881 (Print)
ISSN 1467-789X (Online)

Contents

- 1 On the role and fate of sugars in human nutrition and health. Introduction
A. Palou, M. L. Bonet & C. Picó
- 9 Consumption of sugars and body weight
M. A. van Baak & A. Astrup
- 24 Diabetes, insulin resistance and sugars
M. Laville & J.-A. Nazare
- 34 Added sugars and micronutrient dilution
M. B. E. Livingstone & K. L. Rennie
- 41 Sucrose and dental caries: a review of the evidence
C. A. Anderson, M. E. J. Curzon, C. Van Loveren, C. Tatsi & M. S. Duggal
- 55 Summary and general conclusions/outcomes on the role and fate of sugars in human nutrition and health
L. Arola, M. L. Bonet, N. Delzenne, M. Duggal, C. Gómez-Candela, A. Huyghebaert, M. Laville, P. Lingström, B. Livingstone, A. Palou, C. Picó, T. Sanders, G. Schaafsma, M. van Baak, C. van Loveren & E. M. van Schothorst

On the role and fate of sugars in human nutrition and health. Introduction

A. Palou^{1,2}, M. L. Bonet^{1,2} and C. Picó^{1,2}

¹Molecular Biology, Nutrition and Biotechnology (Nutrigenomics), University of the Balearic Islands (UIB), Palma de Mallorca, Spain; ²CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Palma de Mallorca, Spain

Received 30 October 2008; accepted 18 November 2008

Address for correspondence: Andreu Palou, Universidad de las Islas Baleares, Edificio Mateu Orfila, Cra, Valldemossa Km 7.5, Palma de Mallorca 07122, Spain. E-mail: andreu.palou@uib.es

Summary

The recently implemented European Regulation (EC) No. 1924/2006 on nutrition and health claims made on foods is fuelling scientific research efforts in the food and health arena. Essentially, it is now established that only claims that are scientifically substantiated will be allowed. Because this new legislation covers the idea that foods with health or nutritional claims might be perceived by consumers as having a health advantage over products without claims, it introduces a further requirement (enclosing the new concept of 'nutrient profile') to avoid a situation where claims could mislead consumers when trying to make healthy choices in the context of a balanced diet. Thus, only those foods having an appropriate nutrition profile (composition of different nutrients such as sugars and other substances with particularly relevant nutritional or physiological effects) will be allowed to bear claims. A scientific expert workshop was organized to critically review the available evidence behind current intake recommendations for sugars, focusing on the strength/gaps of the scientific evidence available and the identification of those fields where further research is needed. Work was distributed in the following topics covering potential effects of dietary sugars on (i) body weight control; (ii) diabetes-insulin resistance; (iii) dental health and (iv) micronutrient dilution. New approaches, including intervention studies and the application of nutrigenomic technologies, should be undertaken and interpreted bearing in mind that foods, food components and their combinations can have both positive and negative effects on health, thus requiring benefit–risk analysis.

Keywords: Benefit–risk analysis, carbohydrates, claims, nutrient profile.

obesity reviews (2009) **10** (Suppl. 1), 1–8

Introduction

Carbohydrates are the principal energy source in most Europeans' diet. Carbohydrates contribute to the improvement of the nutritional status and to the maintenance of metabolic homeostasis associated with energy balance, and serve or affect several other functions that, depending on the type and amount of carbohydrate eaten and the balance with other nutrients, range from the physiology and pathology of the large intestine, dental health, and the promotion of, or protection against, the development of chronic non-communicable diseases (such as obesity, cardiovascular disease, type 2 diabetes and some forms of cancer). In

addition, carbohydrates contribute to shaping the sensory qualities of foods, thus determining their acceptability.

The nature and variety of carbohydrate eaten is quite important and increasingly considered, and metabolic fate of carbohydrates is reasonably known (see Fig. 1). However, only a gross distinction among big carbohydrate groups is usually taken into account in nutrition (see Table 1); precise information on more specific subgroups or individually considered chemical species of carbohydrates is only scarcely and sparsely considered, with the probable exception of the more common monosaccharides, disaccharides and starch. Generally speaking, whole grains, legumes, vegetables and fruits are considered the most

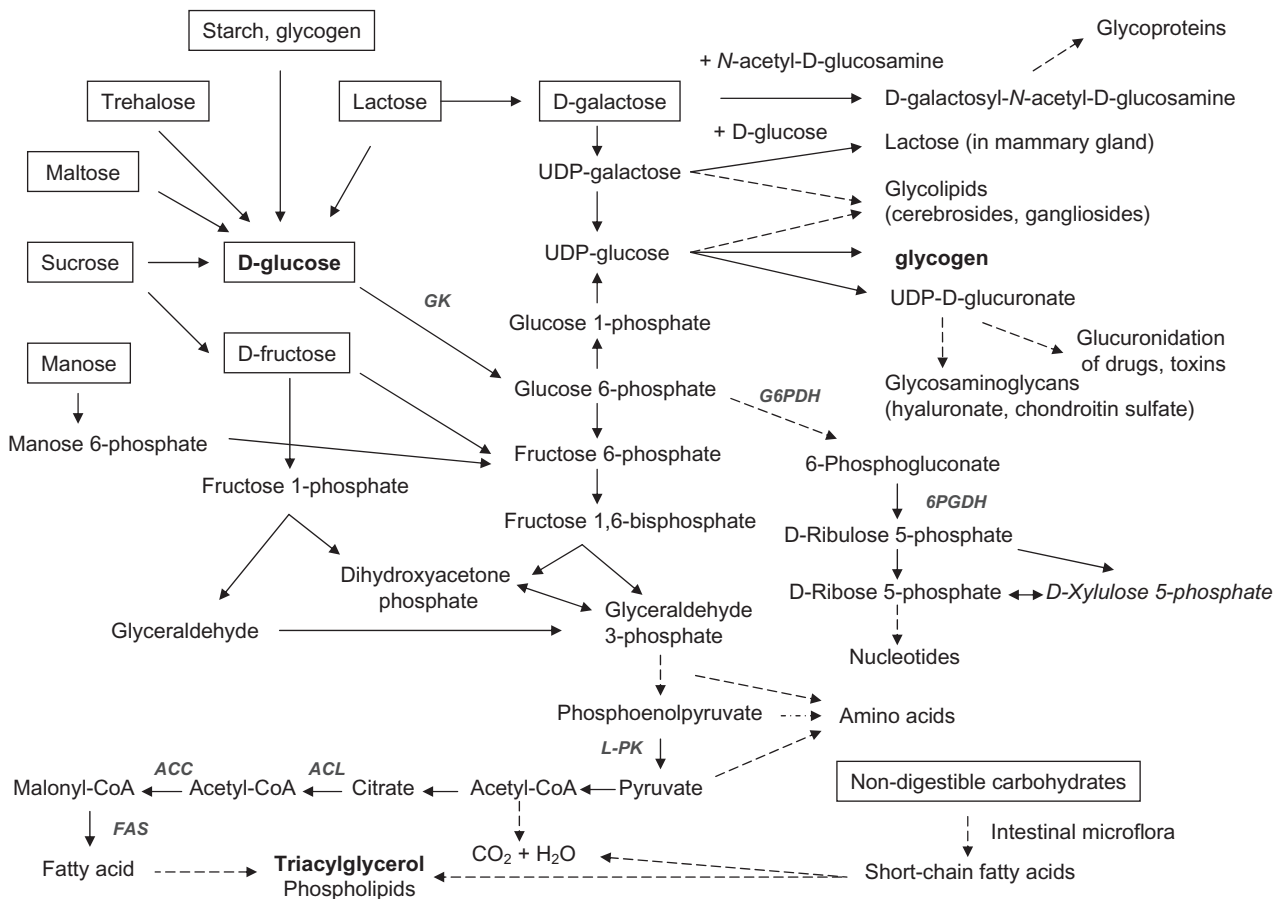


Figure 1 Overview of main pathways involved in the metabolism of carbohydrates from diet. Many carbohydrates present in the diet, besides glucose, particularly polysaccharides, such as starch or glycogen, the disaccharides trehalose, maltose, sucrose and lactose, and the monosaccharides fructose, mannose and galactose, meet their catabolic fate in the glycolytic pathway, after being transformed to one of the glycolytic intermediates. These compounds can be used as fuel to obtain energy, when needed, and excess of energy is stored as glycogen and triacylglycerols. In addition, carbohydrate metabolism provides a variety of precursors for biosynthetic processes. Non-digestible but fermentable carbohydrates (including resistant starch or fructooligosaccharides) can be used by the intestinal microflora which releases metabolites, especially short chain fatty acids (acetate, propionate, butyrate, etc.) into the lumen of the intestine; these compounds are absorbed and can be used as a source of energy. Liver is the major site of carbohydrate metabolism (glycolysis and glycogen synthesis) and triglyceride synthesis (lipogenesis). These pathways are regulated through the acute control of key enzyme activities by means of allosteric and covalent modifications. Moreover, the synthesis of most of these enzymes is regulated in response to dietary status, in which glucose, in particular, plays a crucial role. With the exception of hepatic glucokinase (GK), which is exclusively induced by insulin in hepatocytes, other enzymes indicated in the figure (liver pyruvate kinase [L-PK], glucose 6-phosphate dehydrogenase [G6PDH], 6-phosphogluconate dehydrogenase [6PGDH], ATP citrate lyase [ACL], acetyl CoA carboxylase [ACC], and fatty acid synthase [FAS]) have been shown to be induced at the transcriptional level in response to high glucose and insulin concentrations. This results in the coordinate induction not only of the enzymes of the fatty acid synthesis pathway but also of glycolytic enzymes required for the supply of pyruvate, the precursor of acetyl-CoA, and the enzymes of the pentose phosphate pathways, which are required for the synthesis of NADPH, the essential cofactor for all lipid biosynthesis. The glucose metabolite xylulose 5-phosphate, which is generated by the pentose phosphate pathway in the presence of high glucose, has been proposed to be responsible of the transcriptional effects of glucose promoting lipogenesis.

appropriate sources of carbohydrate as there is wide evidence that these foods, which are rich sources of dietary fibre, are associated with reduced risk of cardiovascular and other chronic diseases (1). On the other hand, evidence has been reported that sugar-sweetened beverages do not induce satiety to the same extent as solid forms of carbohydrate do, and that high consumption of them could promote weight gain. These grounds, together with those

pointing that excess sugars in the diet could be related to other adverse health or nutrition conditions, prompted recent recommendations for the intakes of the different types of carbohydrates by Food and Agriculture Organization/World Health Organization (FAO/WHO) (1,2) and other bodies (3–5). They also prompted measures setting limits for sugar composition to allow food labels or other forms of advertising regarding health claims or

Table 1 The major dietary carbohydrates

Class	Subgroup	Principal components
Sugars (mono- and disaccharides)	Monosaccharides	Glucose, fructose, galactose
	Disaccharides	Sucrose, lactose, maltose, trehalose
Sugar-alcohols (polyols)		Sorbitol, mannitol, lactitol, xylitol, erythritol, isomaltitol, maltitol
Oligosaccharides	Maltooligosaccharides (alpha-glucans)	Maltodextrins
	Non-alpha-glucan oligosaccharides	Raffinose, stachyose, fructo- and galactooligosaccharides, polydextrose, inulin
Polysaccharides	Starch (alpha-glucans)	Amylose, amylopectin, modified starches
	Non-starch polysaccharides	Cellulose, hemicellulose, pectins, hydrocolloids (e.g. gums, mucilages, beta-glucan)

nutritional properties claimed on foods in some countries (6,7), a process that is being implemented in Europe (8,9). However, many questions remain unsolved, in addition to the precision of general recommendations for sugars, as to the specific fate of individual sugars and defined combinations.

In establishing relations between food and health, distinguishing convincing evidence and/or probable evidence from lower levels of evidence becomes very important (2); this is particularly relevant when, in a way or another, conclusions are to be translated into precise recommendations for specific food or food products and/or prescriptive thresholds of nutrients or food components. According to WHO expert group (2), convincing evidence results (i) from the evidence based on epidemiological studies showing consistent associations between exposure and disease, with little or no evidence of the contrary; (ii) from the availability of a substantial number of studies, including prospective observational studies and, where relevant, randomized controlled trials of sufficient size, duration and quality, showing consistent effects and (iii) from the associations having biological plausibility (2).

The European Regulation No. 1924/2006 on nutrition and health claims made on foods and the concept of nutrient profiles

In Europe, when dealing with food the emphasis is nowadays placed on the food potential to promote health, improve well-being and reduce the risk of illness. The relationship between optimum nutrition and a healthy life is gaining public acceptance and is supported by scientific developments (e.g. see Palou *et al.* (10,11) and references therein). Consumers are increasingly health-conscious and, at the same time, the industry seeks to take advantage of the developments in food science, and is increasingly investing in innovative projects in the area of food and health. On the one hand, only a food that successfully conveys its health benefits in a meaningful way to the consumer is eventually an investment incentive for the industry; on the

other hand, for consumers to believe in health claims made on food, these claims must be based on solid science. All in all, the need for credible health and nutritional claims arose and prompted the final agreement on a new general Regulation in Europe (9), which harmonizes all related legislation in all European Union countries. This Regulation – (EC) No. 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods – has already been implemented since July 2007 in a transition period of a few years, and is accompanied by founded expectations to introduce very important economic, public health and social consequences (9). The more controversial issue has been, and perhaps still is, that of ‘nutrient profiles’, a concept that was finally incorporated into the regulatory text only after about 3 years of controversy in the European Parliament and intense discussions among stakeholders (9).

The introduction of the concept of ‘nutrient profiles’ arose from the realization that foods promoted with claims might be perceived by consumers as having a health advantage over products without claims, which may encourage their consumption (12). To avoid a situation where health claims could mislead consumers when trying to make healthy choices in the context of a balanced diet and situations where the nutrition or health claims may mask the overall nutritional value of a food product, it was considered appropriate to impose certain restrictions as regards the products bearing claims. Hence, it was established that only food complying with ‘appropriate’ nutrient profiles will be allowed to bear nutrition or health claims (9). Nutrient profiles shall be based on scientific knowledge about the relationships between diet, nutrition and health, and shall be updated to take into account relevant scientific developments (9).

Nutrient profiles are yet to be defined in full and are expected to be a concept whose practical application will be in progressive evolution. However, it has been left clear (9) that, when setting nutrient profiles, it should be taken into account the role and importance of the food (or of the categories of food) and its contribution to the diet of the

population in general or, as appropriate, of certain risk groups including children; the overall nutritional composition of the food; and the presence of nutrients that have been scientifically recognized as having an effect on health. Food components specifically mentioned in the Regulation are fat, saturated fat, trans-fatty acids, salt/sodium and sugars, excessive intakes of which in the overall diet are not recommended (9). Other components mentioned are poly- and mono-unsaturated fats, carbohydrates other than sugars, vitamins, minerals, protein and fibre (9).

The introduction of the concept of nutrient profiles has important implications for food developments in general, and for developments dealing with sugar-containing foods in particular.

Carbohydrates and sugars in foods

Carbohydrates can be classified based on chemistry into three main groups according to the degree of polymerization: sugars, consisting of 1 or 2 monomers; oligosaccharides, consisting of 3–9 monomers; and polysaccharides, consisting of 10 or more monomers. Carbohydrates within each group are further distinguished depending on the nature of the individual monomers and the type of linkage (alpha and non-alpha) among them. Thus, a range of components such as polyhydroxy aldehydes, ketones, alcohols and acids, as well as their derivatives and polymers are included in the group carbohydrates (see Table 1) (2,13,14).

In Europe, for labelling purposes, the meaning of 'sugars' in the legislation refers to all monosaccharides and disaccharides present, from whatever source, in a food excluding polyols (which are alcohols of sugars) (15). The three principal monosaccharides in food are glucose, fructose and galactose, which are the building blocks of naturally occurring di-, oligo- and polysaccharides. The principal disaccharides are sucrose (α -Glc(1-2) β -Fru), the usual sugar in plant foods (typically extracted from cane or beet) and lactose (β -Gal(1-4)Glc), which is the main sugar in milk.

Apart from the orthodox, chemistry-founded, terminology in the literature, a number of more or less puzzling terms to describe carbohydrate (in general) and sugar (in

particular) in foods can be found, such as prebiotic, resistant starch, dietary fibre, available and unavailable carbohydrate, complex carbohydrate, glycaemic, whole grain, sugars, single sugars, free sugars, added sugars, intrinsic and extrinsic sugars and total sugars (see Cummings and Stephen (13)). These terms are used with the aim to distinguish with respect to components, their state and origin, and often for food labelling purposes. For example, the term 'intrinsic' sugar refers to sugars naturally occurring in foods, whereas the term 'added sugars' usually refers to sucrose, fructose, glucose, starch hydrolysates and other isolated sugar preparations consumed as such or added during food production or preparation. The relative usefulness of carbohydrate terminology to describe, measure and label sugars and carbohydrate in general in foods has been reviewed recently (13).

Reported recommendations and challenges

Various national and international bodies have provided assessment and guidance on desirable dietary intakes of carbohydrates in general and sugars in particular ((1–5,16) and see Table 2).

First in 1980 (16) and later in 1998 (14), FAO and WHO already reviewed the role of carbohydrates as determinants of human health and disease as part of an effort to further understand the relationship between diet and various non-communicable diseases, including obesity, type II diabetes, coronary heart disease and some forms of cancer. It was concluded that carbohydrates are not only an energy source; they also have important impacts on the maintenance of health (14,16). Two other instances of a joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases was reported in 2000 (2,17). Emphasized in these reports were the recommendations to maximize the intake of minimally processed carbohydrates while minimizing that of free sugars. It was further indicated that regular consumption of whole-grain cereals, fruits and vegetables, which are preferred sources of non-starch polysaccharides, was likely to reduce the risk of diet- and nutrition-related non-communicable diseases (2).

	Total carbohydrates (% Energy)	Added sugars (% Energy)	Dietary fibre (g d ⁻¹)
WHO	55–75	<10	>25
USA	45–65	–	25–38
France	50–55	<10	25–30
UK	47	<10	>18
Nordic countries	50–60	<10	25–35
Eurodiet	>55	<4 occasions/day	>25
Spain	>50	–	>25

Table 2 Dietary recommendations of carbohydrates for adults from different bodies

Very recently, the issue of carbohydrates in human nutrition has been updated by FAO/WHO, focusing on some identified key issues: terminology and classification, measurement, physiology, carbohydrates and diseases (obesity, diabetes mellitus, cardiovascular diseases and cancer), and glycaemic index and glycaemic load (13,17–22). These updated reviews applied previously established criteria (2) to describe strength of evidence for drawing conclusions about associations between diet and disease. The joint FAO/WHO Scientific Update on Carbohydrates in Human Nutrition enabled some firm conclusions to be drawn and identified a number of areas where more research is required to enable definitive recommendations (1).

A population nutrient intake goal for free sugars of less than 10% of total energy was proposed by the WHO and FAO already in 2003 (2) and in their recently updated recommendations (17), free sugars referring to all monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, plus sugars naturally present in honey, syrups and fruit juices. The rationale for this recommendation included the recognition that high intakes of free sugars threaten the nutrient quality of diets by providing significant energy without specific nutrients, and – noting that free sugars contribute to the overall energy density of diets and might promote a positive energy balance – that restriction of free sugars is likely to contribute to reducing the risk of unhealthy weight gain. Different types of studies were considered in making this recommendation (reviewed in (1,17,18,20–23)). Acute and short-term studies in human volunteers have shown increased total energy intake when the energy density of the diet is increased, whether by free sugars or fat. Diets that are limited in free sugars have been shown to reduce total energy intake and induce weight loss. There is evidence that drinks that are rich in free sugars increase overall energy intake by interfering with appetite control mechanisms (see Ludwig (23) and references therein). A randomized trial showed that consumption of soft drinks rich in free sugars results in higher energy intake and body weight gain when compared with consumption of energy-free drinks that are artificially sweetened (24). Children with a high consumption of soft drinks rich in free sugars are more likely to be overweight and to gain excess weight (25). However, setting up a specific threshold based on substantiated scientific evidence is difficult, and the Consultation recognized that a population goal for free sugars of less than 10% of total energy is controversial (2).

Very recently, the European Food Safety Authority-scientific panel NDA (Nutrition, dietetic foods and Allergies) has delivered its opinion (8) on sugars when considering the setting of nutrient profiles for foods bearing nutrition and health claims pursuant to article 4 of the regulation (EC) No. 1924/2006 (9), which foresees that the European Commission shall establish (by 19 January 2009)

specific nutrient profiles that foods must respect in order to bear nutrition and health claims. Main conclusions in this opinion (see EFSA (8) and references therein) are as follows. Increased risk of dental caries in children is associated with a high frequency (more than about 4 times daily) of intake of cariogenic sugars (mainly sucrose, glucose and fructose) rather than with the total amount of dietary sugars. The evidence indicates that frequent consumption of sweets and confectionery products and sugar-containing drinks is associated with a higher risk of caries. The evidence relating high intake of sugars (mainly as added sugars), compared with high intakes of starch, to weight gain is inconsistent. However, there is some evidence that sugar-sweetened beverages do not induce satiety to the same extent as solid forms of carbohydrate, and that high intakes of sugars in the form of sugar-sweetened beverages might contribute to weight gain. There is some evidence that high intakes of added sugars, particularly from low-nutrient-density foods, might be associated with a decrease in the nutrient density of the diet ('nutrient dilution') due to displacement of nutrient rich foods (26); however, the evidence for an association of micronutrient dilution with added sugar intake is limited and inconsistent (8).

Dietary recommendations in general are strongly influenced by the realization that changes in diets and patterns of work and leisure – often referred to as the 'nutrition transition' – are already contributing to the causal factors underlying non-communicable diseases (2). The pace of these changes seems to be accelerating, especially in the low-income and middle-income countries. The prevalence of overweight and obesity in both children and adults has increased rapidly around the world in recent decades reaching epidemic proportions, particularly in those countries that are going through rapid economic transition. The dietary changes that characterize the 'nutrition transition' include shifts in the structure of the diet towards a higher energy density diet with a greater role for fat and added sugars in foods, increased saturated fat intake (mostly from animal sources), and reduced intake of complex carbohydrates, dietary fibre, fruit and vegetable (2,16). A precise contribution of changes in carbohydrate (and the different types of it) intake to the 'nutrition transition' cannot be ruled out, but it is essentially unknown.

Most information about the relationship between dietary carbohydrates/sugars and health comes from observational epidemiological studies that cannot prove causality and in which it is conceivable that, at least in part, carbohydrate in diets simply act as a marker of some other factors. For real progress in establishing links between carbohydrate/sugar intake and health, high-quality randomized controlled nutritional intervention trials are needed. Such trials should ideally contemplate long-term effects and consider not only the total amount, but also the frequency of carbohydrate

consumption, as this might be one key point (particularly for free sugars) that has insufficiently been addressed so far. Moreover, because specific carbohydrates, as other dietary chemicals, can entail both health benefits and risks, there is the need to obtain more complete biomarker profiles, rather than focusing on individual biomarkers or end-points, in nutrition research dealing with them; in this context, approaches involving the use of post-genomic technologies might be particularly useful. In addition, specific effects of carbohydrates on regulatory circuitries controlling physiological responses and gene expression have progressively been unveiled and need to be understood at the molecular level. For instance, the increasing incidence of obesity and related diseases worldwide is nowadays enhancing an intensive study of the role of carbohydrates as potential regulators of energy balance (e.g. by regulating appetite and/or energy expenditure) or other processes specifically involved in obesity development (see 27–29), where specific cause–effects and mechanisms behind can be identified for defined chemical species and combinations. All in all, it is recognized that new studies are required to help setting up more precise figures for sugar and carbohydrate intake recommendations.

Recent revisions did not concentrate on identifying priority research aspects that could lead to the formulation of more precise and substantiated recommendations. At this respect, let's not forget this sort of bottleneck is created by traditional limitations of nutrition and food research (30,31), the typical approaches to energy adjustment, the misreporting of food/nutrients intake, and the ambiguity of reported specifications of the foods tested in different studies, altogether with other methodological or approaching problems, including cultural aspects, which identification preserve further progress in this area. On the one hand, new nutrigenomic technologies can add a lot; on the other hand, new approaches can be applied under the view that foods and food components can have both positive and/or negative effects on our health, resulting in benefits and risks. At present these are evaluated in largely separated trajectories while we have recently proposed and argued for an integrated evaluation of risk and benefit of food components and foods, which will allow better management and, especially, communication to the benefit of the consumer (40).

Revising and reflecting on the new challenges

A scientific expert workshop ‘On the role and fate of sugars in human nutrition and health’ was organized in September 2007. The aim was to critically review the available evidence behind current intake recommendations for sugars, and to identify priority research aspects that could lead to the formulation of more precise and substantiated recommendations. The group agreed on some particularities for

the approach in order not to repeat what other reviews have already done. Focusing on the strength/gaps of evidence and suggesting new fields of research was identified as the way to do so. Therefore, the following working method was agreed on (i) to identify and review the available literature; (ii) to evaluate the relative strength of evidence (indicating, for example, the presence or lack of randomized and controlled human intervention studies, etc.) and (iii) to indicate possible new fields of research. Work was distributed in the following topics:

1. Dietary sugars and obesity.
2. Dietary sugars and diabetes-insulin resistance.
3. Dietary sugars and dental health.
4. Dietary sugars and micronutrient dilution.

It is clear that the aetiology of obesity is multifactorial, involving social, genetic and environmental factors. Nutrition, in particular during development, can alter organ function and thereby prevent or predispose individuals to obesity and related diseases. However, knowledge on precise causal food-related determinants of weight gain is both scarce and sparse, and no specific nutrients or food components have been involved so far (with the probable exception of epigenetic-driving predispositions elicited by breast milk components (32–34)). As sugar-sweetened beverages (SSB) account for an increasingly significant proportion of total energy intake in most developed societies, these beverages have been targeted as one of the potential guilty in the growing rates of obesity. There is evidence that SSB do not induce satiety to the same extent as solid forms of carbohydrate, and this and other mechanisms have been proposed to explain a possible association between SSB consumption and overweight and obesity (26,35,36). Some recent meta-analysis of published studies support such an association and hence recommendations to reduce population SSB consumption (37,38). However, much of the evidence comes from observational rather than intervention studies, and thus permits no conclusions about causal links (35,39). The role of different types of carbohydrates on eating behaviour is not expected to have large effects on long-term energy homeostasis as indirectly deduced from intervention studies (26). It has even been suggested that emphasis on reducing extrinsic sugars intakes may be counterproductive to attempts to reduce proportional fat intake and body weight (30,31). Thus, the evidence of an obesogenic effect of SSB consumption is suggestive but not conclusive, raising the question as to what extent and how can it be translated to specific standards. This is addressed in the review paper by Van Bach and Astrup in this supplement (41).

Obesity and *insulin-resistance* are often associated phenomena. The relation of free sugar consumption and health-related issues seems clear for diabetic patients, but evidence for the rest of population is scarce. The reference

to a mixed and varied, rich in vegetables, balanced diet appears repeatedly. Can we go further with more precise recommendations? This is addressed in the review paper by Laville and Nazare in this supplement (42).

It is generally accepted that the frequency of consumption of sugars has an impact on *dental caries* whereas the discussion continues as to whether the actual amount consumed has any such impact. The importance of other factors (fluoride) overriding the effects of diet and sugar consumption is a matter of some confusing situation. Can we combine frequency and load in a quantitative recommendation? This is addressed in the review paper by Anderson *et al.* in this supplement (43).

Whether a high intake of sugars can compromise desirable *micronutrient* intakes is also a matter of intense debate. High-quality data on the issue of micronutrient dilution is scarce, and the available evidence needs to be critically examined to evaluate the nutritional significance and, if possible, to estimate the range of sugars intake that can be compatible with micronutrient adequacy. Does the available evidence allow obtaining firm conclusions on an optimal level or threshold of added sugars intake for micronutrient adequacy? This is addressed in the review paper by Livingstone and Rennie in this supplement (44).

Certainly, in our first round difficulties were foreseen to find an overall conclusion for all those areas of work. For this reason, the working group agreed that, at the pre-publication phase, a workshop with about 20 selected invitations would round-up an opportunity to present the final conclusions and consensus of the group together with the collection for new ideas and suggestions that, all together, can contribute to a reflective position on the dietary sugars, thoughts and gaps (see conclusions in this supplement (45)).

Conflict of Interest Statement

The authors declare no conflicts of interests.

Acknowledgements

Spanish Government (grant AGL2006-04887/ALI). Our Laboratory is a member of the European Research Network of Excellence NuGO (The European Nutrigenomics Organization, EU Contract: No. FP6-506360). The CIBER de Fisiopatología de la obesidad y nutrición is an initiative of the ISCIII.

References

1. Mann J, Cummings JH, Englyst HN, Key T, Liu S, Riccardi G, Summerbell C, Uauy R, van Dam RM, Venn B, Vorster HH, Wiseman M. FAO/WHO scientific update on carbohydrates in human nutrition: conclusions. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S132–S137.

2. WHO. Diet, nutrition, and the prevention of chronic diseases. Report of A Joint WHO/FAP Expert Consultation. *WHO Technical Report Series No. 916*. World Health Organization: Geneva, Switzerland, 2003.

3. ANC. Apports nutritionnels conseillés pour la population française. 3e édition, coordonnateur Alexy U. Kersting M Schultze-Pawlitschko V. Two approaches to derive a proposal for added sugars intake for German children and adolescents. *Public Health Nutr* 2003; **6**: 697–702.

4. DACH. *Referenzwerte für die Nährstoffzufuhr*. 1. Auflage. Deutsche Gesellschaft für Ernährung, Österreichische Gesellschaft für Ernährung, Schweizerische Gesellschaft für Ernährung, Schweizerische Vereinigung für Ernährung: Umschau Braus, Frankfurt am Main, 2000.

5. NNR. Nordic Nutrition Recommendations. *Integrating Nutrition and Physical Activity*. Nord 2004:13. Nordic Council of Ministers: Copenhagen, 2004.

6. SNF. Swedish National Food Administration. *Livsmedelsverkets Föreskrifter Omanvändning av Viss Symbol LIVSFS 2005:9 (Ordinance with Conditions for the Use of Certain Symbols)* (In Swedish). Swedish National Food Administration: Stockholm, 2005.

7. AFSSA. *Definition of Nutrient Profiles for the Validation of Nutrition and Health Claims: Afssa Proposals and Arguments*. Agence Française de Sécurité Sanitaire des Aliments: Paris, 2008.

8. EFSA. (NDA-Scientific-Panel). The setting of nutrient profiles for foods bearing nutrition and health claims pursuant to article 4 of the regulation (EC) No 1924/2006. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies (Adopted on 31 January 2008). *EFSA J* 2008; **644**: 1–44.

9. EC. Corrigendum to Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods (Official Journal of the European Union L 404 of 30 December 2006). *Off J Eur Union* 2007; **L12**: 3–18.

10. Palou A, Pico C, Bonet ML. Food safety and functional foods in the European Union: obesity as a paradigmatic example for novel food development. *Nutr Rev* 2004; **62**: S169–S181.

11. Palou A, Serra F, Pico C. General aspects on the assessment of functional foods in the European Union. *Eur J Clin Nutr* 2003; **57**(Suppl. 1): S12–S17.

12. Palou A. European Food Law is nourished by credible health claims made on Foods (Editorial). *Eur Food Feed Law Rev* 2007; **4**: 1–2.

13. Cummings JH, Stephen AM. Carbohydrate terminology and classification. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S5–S18.

14. FAO/WHO. Joint FAO/WHO expert consultation. Carbohydrates in human nutrition. Food and Agriculture Organization, World Health Organization. *FAO Food and Nutrition Paper* 66. Rome, 1998.

15. EC. Council Directive 90/496/EEC of 24 September 1990 on nutrition labelling for foodstuffs. *Off J* 1990; **L276**: 40–44.

16. WHO. Diet, nutrition and the prevention of chronic diseases. Report of a WHO Study Group. *WHO Technical Report Series No. 797*. World Health Organization, Geneva, 1980.

17. Nishida C, Martinez Nocito F. FAO/WHO scientific update on carbohydrates in human nutrition: introduction. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S1–S4.

18. Elia M, Cummings JH. Physiological aspects of energy metabolism and gastrointestinal effects of carbohydrates. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S40–S74.

19. Englyst KN, Liu S, Englyst HN. Nutritional characterization and measurement of dietary carbohydrates. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S19–S39.

20. Key TJ, Spencer EA. Carbohydrates and cancer: an overview of the epidemiological evidence. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S112–S121.
21. Mann J. Dietary carbohydrate: relationship to cardiovascular disease and disorders of carbohydrate metabolism. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S100–S111.
22. Venn BJ, Green TJ. Glycemic index and glycemic load: measurement issues and their effect on diet-disease relationships. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S122–S131.
23. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* 2002; **287**: 2414–2423.
24. Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 weeks of supplementation in overweight subjects. *Am J Clin Nutr* 2002; **76**: 721–729.
25. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet* 2001; **357**: 505–508.
26. van Dam RM, Seidell JC. Carbohydrate intake and obesity. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S75–S99.
27. Drewnowski A, Kurth C, Holden-Wiltse J, Saari J. Food preferences in human obesity: carbohydrates versus fats. *Appetite* 1992; **18**: 207–221.
28. Liu S, Manson JE. Dietary carbohydrates, physical inactivity, obesity, and the ‘metabolic syndrome’ as predictors of coronary heart disease. *Curr Opin Lipidol* 2001; **12**: 395–404.
29. Wylie-Rosett J, Segal-Isaacson CJ, Segal-Isaacson A. Carbohydrates and increases in obesity: does the type of carbohydrate make a difference? *Obes Res* 2004; **12**(Suppl. 2): 124S–129S.
30. Gibson SA. Are diets high in non-milk extrinsic sugars conducive to obesity? An analysis from the Dietary and Nutritional Survey of British Adults. *J Hum Nutr Diet* 2007; **20**: 229–238.
31. Gibson SA. Commentary on Gibson SA. (1996). Are diets high in non-milk extrinsic sugars conducive to obesity? An analysis from the Dietary and Nutritional Survey of British Adults. *Journal of Human Nutrition and Dietetics*; **9**: 283–292. *J Hum Nutr Diet* 2007; **20**: 239–240.
32. Pico C, Oliver P, Sanchez J, Miralles O, Caimari A, Priego T, Palou A. The intake of physiological doses of leptin during lactation in rats prevents obesity in later life. *Int J Obes (Lond)* 2007; **31**: 1199–1209.
33. Sanchez J, Priego T, Palou M, Tobaruela A, Palou A, Pico C. Oral supplementation with physiological doses of leptin during lactation in rats improves insulin sensitivity and affects food preferences later in life. *Endocrinology* 2008; **149**: 733–740.
34. Palou A, Oliver P, Sanchez J, Priego T, Pico C. The role of breast milk leptin in the prevention of obesity and related medical complications in later life. In: Cerf M (ed.). *Developmental Programming of Diabetes and Metabolic Syndrome*. Transworld Research Network: Kerala, 2008, pp. 39–49.
35. Pereira MA. The possible role of sugar-sweetened beverages in obesity etiology: a review of the evidence. *Int J Obes (Lond)* 2006; **30**: S28–S36.
36. Bachman CM, Baranowski T, Nicklas TA. Is there an association between sweetened beverages and adiposity? *Nutr Rev* 2006; **64**: 153–174.
37. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health* 2007; **97**: 667–675.
38. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr* 2006; **84**: 274–288.
39. Drewnowski A, Bellisle F. Liquid calories, sugar, and body weight. *Am J Clin Nutr* 2007; **85**: 651–661.
40. Palou A, Pico C, Keijer J. Integration of Risk and Benefit Analysis. The Window of Benefit as a New Tool? *Crit Rev Food Sci Nutr* 2009 (in press).
41. van Baak MA, Astrup A. Consumption of sugars and body weight. *Obesity Reviews* 2009; **10**(Suppl. 1): 9–23.
42. Laville M, Nazare J.-A. Diabetes, insulin resistance and sugars. *Obesity Reviews* 2009; **10**(Suppl. 1): 24–33.
43. Anderson CA, Curzon MEJ, Van Loveren C, Tatsi C, Duggal MS. Sucrose and dental caries: a review of the evidence. *Obesity Reviews* 2009; **10**(Suppl. 1): 41–54.
44. Livingstone MBE, Rennie KL. Added sugars and micronutrient dilution. *Obesity Reviews* 2009; **10**(Suppl. 1): 34–40.
45. Arola L, Bonet ML, Delzenne N, Duggal MS, Gómez-Candela C, Huyghebaert A, Laville M, Lingström P, Livingstone B, Palou A, Picó C, Sanders T, Schaafsma G, van Baak M, van Loveren C, van Schothorst EM. Summary and general conclusions/outcomes on the role and fate of sugars in human nutrition and health. *Obesity Reviews* 2009; **10**(Suppl. 1): 55–58.

Consumption of sugars and body weight

M. A. van Baak¹ and A. Astrup²

¹NUTRIM, Department of Human Biology, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; ²Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen, Frederiksberg, Denmark.

Received 30 October 2008; revised 28 November 2008; accepted 28 November 2008

Address for correspondence: Professor MA van Baak, Department of Human Biology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands. E-mail: m.vanbaak@hb.unimaas.nl

Summary

The role of dietary sugars in the current obesity epidemic is much debated and opposing views can be found in the lay as well as scientific literature. Here we have reviewed the recent scientific literature on consumption of sugars and body weight. Main focus was on three questions: (i) What is the evidence that intake of dietary sugars is associated with higher body weight than intake of non-sugar carbohydrates? (ii) What is the evidence that sugars in liquid form are associated with higher body weight than sugars in solid form? (iii) What is the evidence that diets with a low glycaemic index (GI) or glycaemic load (GL) are associated with lower body weight than diets high in GI or GL? We conclude that (i) there is insufficient evidence that an exchange of sugar for non-sugar carbohydrates in the context of a reduced-fat *ad libitum* diet or energy-restricted diet results in lower body weights; (ii) observational studies suggest a possible relationship between consumption of sugar-sweetened beverages and body weight, but there is currently insufficient supporting evidence from randomized controlled trials of sufficient size and duration; (iii) at this moment there is insufficient evidence to support a difference between liquid and solid sugar intake in body-weight control and (iv) there is some, although not consistent, evidence for a lower body weight on diets with a lower GL, but the effect is likely to be small. There is currently no convincing evidence for a role of GI independent of GL.

Keywords: Diet, obesity, sugars, weight gain.

obesity reviews (2009) **10** (Suppl. 1), 9–23

Introduction

The role of dietary macronutrient consumption in the current obesity epidemic remains controversial. Although all sources of energy consumed contribute to weight gain and the development of obesity if consumed in excess of energy need, high fat consumption as well as high carbohydrate, and specifically high sugar consumption, are often considered particularly harmful with respect to energy balance disturbances due to their specific properties being beyond a source of energy. These specific properties relate to postprandial metabolism, the balance between nutrient storage and oxidation, and the effects on hunger and satiety, and hence on caloric intake and energy balance.

In 2003, the role of sugars in overweight and obesity was reviewed by Saris (1). The main conclusions from this review were that the fat content of the diet is the most

important contributor to passive over-consumption and that the carbohydrate content, regardless of carbohydrate type, is relatively benign in this respect, with little evidence for direct negative effects of dietary sugar on body weight. This conclusion was based on the following evidence: (i) cross-sectional studies showed an inverse relationship between sucrose intake and body weight or body mass index (BMI), as well as between sucrose intake and total fat intake; (ii) weight-loss studies with different types and amounts of carbohydrates including high and low sucrose did not indicate that weight loss was impaired by high-sucrose, energy-restricted diets; and (iii) results from the Carbohydrate Ratio Management in European National diets (CARMEN) multicentre trial, showing no difference in weight changes between fat-reduced high simple carbohydrate or high complex carbohydrate diets. A need for long-term *ad libitum* studies on the effects of different types

of carbohydrates on body-weight control was expressed with special attention to the confounding effects of other macronutrients as well as the type of food (solid or liquid) (1).

Since then, the discussion about the role of sugars in the obesity epidemic has continued and has been fuelled by the popularity of low-carbohydrate diets, such as the Atkins diet, discussions about the contribution of sugars to energy density of low-fat alternatives for high-fat foods, the importance of the glycaemic response for postprandial metabolism and appetite regulation, the use of high fructose corn syrup (HFCS) as sweetener instead of sucrose, and potential differences between the intake of sugars in the form of solid or liquid products.

This review intends to discuss the situation 5 years later and to weigh the strength of the evidence for a role of sugars in body-weight management. It will focus on the influences of sugars compared with starches, of sugar-sweetened beverages, of the replacement of carbohydrates by fat or protein, and on the role of glycaemic index (GI) and glycaemic load (GL) in body-weight control.

Sugars can be grouped into monosaccharides (glucose, fructose and galactose), disaccharides (sucrose, lactose, maltose and trehalose) and polyols or sugar-alcohols (sorbitol, mannitol, lactitol, xylitol, erythritol, isomalt and maltitol) (2). HFCS is a mixture of free glucose and fructose (usually with 42% or 55% fructose), which has increasingly replaced sucrose (50% fructose, 50% glucose as disaccharide) in many foods and most sweetened beverages in the USA. Outside the USA sucrose continues to be the primary caloric sweetener. For the purpose of this review, the term 'sugars' is used for all sugars from all sources other than polyols. No specific attention is paid to HFCS. A recent review by an expert panel in the USA has concluded that claims that the introduction of HFCS has increased the ratio of fructose to glucose in the diet or the sweetness of the diet are not substantiated and even contradicted by the available evidence (3).

Carbohydrate intake and body weight

There is considerable evidence that macronutrients differ in their capacity to influence appetite and satiety, with fat being the least satiating and proteins the most. Therefore, changes in the macronutrient ratios of the diet may contribute to more effective prevention of weight gain and achievement of weight loss (4).

From a recent review of epidemiological studies, Gaesser concluded that most cross-sectional population studies show an inverse relationship between carbohydrate intake and BMI in men as well as women, which could not be entirely explained by (selective) underreporting, lower total energy intake, higher physical activity or higher fibre intake (5). Van Dam and Seidell concluded from a review of the

literature up till 2006 that included randomized intervention studies, observational studies and results from the US National Weight Control Registry, that there is no strong evidence that either increasing or decreasing the energy percentage of carbohydrate in the diet by itself has an important effect on body weight and that the quality of the carbohydrates and the ratio of other macronutrients in the diets may be more important (4).

Total carbohydrate vs. fat and protein intake

A number of meta-analyses of intervention studies, although not all randomized controlled trials (RCTs), have concluded that a reduction of the fat content of the diet results in a moderate weight loss in overweight and obese people (6–8). Yu-Poth *et al.* concluded from a meta-analysis of 37 randomized dietary intervention studies with reduced (saturated) fat content that every 1% decrease in energy as total fat was associated with 0.28 kg reduction in body weight (8). Similarly, a 10.2% lower dietary fat content was associated with a 3.2 kg greater body-weight loss in the meta-analysis of 19 *ad libitum* dietary interventions with reduced fat intake by Astrup *et al.* (6). Nine of these studies were also included in the Yu-Poth meta-analysis (8). In many of the studies included in these analyses, reduction of the dietary fat content was associated with an increase in the carbohydrate content of the diet. Findings from the Women's Health Initiative Trial, comparing a low-fat carbohydrate-rich diet with a control diet higher in fat, suggest that an *ad libitum* reduced-fat (24–29% of energy from fat) diet resulted in modest but greater weight loss during the first year of the trial and less weight regain over 7.5 years than the higher fat (35–37% of energy from fat) diet, despite the fact that neither group was interested to lose weight (9). The difference in weight loss between groups after the first year was 1.9 kg ($P < 0.001$) and 0.4 kg ($P = 0.01$) after an average of 7.5 years. Compliance to the low-fat diet was obviously poor during such a long period, but *post hoc* analysis of self-reported diet suggested that those who had reduced their fat intake had gained ~2 kg less than the control group after 7 years. Similarly, two large multi-centre, randomized studies (i.e. the Diabetes Prevention Program and the Finnish Diabetes Prevention Study) have demonstrated that greater weight loss can be achieved in groups consuming calorie-controlled low-fat, high-carbohydrate diets compared with controls receiving standard lifestyle recommendations (10,11).

Recent studies suggest that an exchange of fat for protein results in more pronounced weight loss under *ad libitum* conditions or better weight maintenance after weight loss in studies up to 6 months (12). As with many other diets, the long-term (≥ 1 year) effects of low-fat high-protein diets compared with low-fat high-carbohydrate diets are quite

small and often not statistically significant (13–16), which may in part be related to low long-term compliance to the diets in some of these studies. In the studies by Due *et al.* (16) and Brinkworth *et al.* (14), both with relatively good compliance, the weight loss difference was 1.9 and 1.7 kg, respectively, between the HP and HC groups, whereas it was 0.2 and 1.1 kg in the two studies with low compliance (13,15). Clifton *et al.* found that 12 months after a 12-week intensive weight loss programme with a high-protein or high-carbohydrate diet, there was no significant difference in weight change between the groups, although a higher reported protein intake at follow-up was associated with significantly more weight loss (3.1 kg difference between upper tertile (88 [g protein] d⁻¹) and two lowest tertiles) (15).

On the other hand, energy-restricted low carbohydrate diets are currently very popular in many countries as weight loss strategies. A quantitative meta-analysis in 2006 on five RCTs (Table 1) showed an overall difference in weight loss of -3.3 kg (95% confidence interval [CI] -5.3, -1.4 kg) in favour of the low-carbohydrate diets after 6 months. After 12 months, the difference was no longer statistically significant (-1.0 kg, 95% CI -3.5, 1.5 kg) (17).

Three additional trials have been published in 2007 (Table 1) (18–20). The first trial showed that weight loss after 3 months was more pronounced with an *ad libitum* low-carbohydrate diet than with a standard reduced fat, low GI energy-restricted (2.1 MJ d⁻¹ deficit) diet (-6.9 vs. -2.1 kg, $P < 0.003$) in 26 type 2 diabetic and control subjects (18), confirming the short-term effectiveness of low-CHO diets for weight loss. Another study involved gastric bypass patients. Thirty-two surgical patients were randomized postoperatively to a low-fat (<35 g d⁻¹, 50–60 [g protein] d⁻¹) diet or a low-carbohydrate diet (based on the South Beach diet) for 12 months. BMI was reduced by 14% in the low-fat group and by 17% in the low-carbohydrate group ($P = 0.15$) (20), confirming the lack of long-term efficacy of low-CHO diets.

A third trial by LeCheminant *et al.* compared the effects of a low-fat (55% CHO, 25% fat, 20% protein) and low-carbohydrate (27% CHO, 44% fat, 25% protein) diet on body weight over a 6-month weight loss maintenance period after diet-induced weight loss in overweight and obese subjects. Weight change over these 6 months was 0.1 kg in the low-CHO group and -0.3 kg in the low-fat group (not significant) (19). More data are needed to further assess the value of low-CHO diets for prevention of weight regain.

A low-carbohydrate diet cannot be recommended, because it is associated with adverse effects including tissue breakdown, dehydration and electrolyte imbalance, and gives rise to headache, muscle weakness and cramps, diarrhoea and reduced exercise performance (21).

Sugar intake and body weight

A recent cross-sectional study in 1294 British children and adolescents of 7–18 years old showed that there was a weak inverse correlation between the BMI z-score and the percentage energy of non-milk extrinsic sugars (NMES) in the diet, which was attenuated but not reversed after adjusting for underreporting and dieting (22). A similar analysis in 2197 British adults also revealed an inverse association between percentage of energy from NMES and BMI (23). These studies confirm the inverse relationship between sugar intake and BMI in cross-sectional studies that has been reported in previous reviews of the literature (1,5,24,25).

In the America on the Move Family Study overweight children ($n = 95$) tried to reduce their sugar intake by 420 kJ d⁻¹ as part of a 24-week intervention to promote small increases in physical activity and reductions in sugar intake. This goal was attained on 78% of study days. No significant change in sugar consumption was reported in the control group ($n = 89$). Data on accompanying dietary changes in both groups were not provided. Despite the fact that children in the intervention group also increased their average number of steps more than those in the control group, BMI changes did not differ between groups (26).

Sugar intake vs. intake of non-sugar carbohydrates

An overview of the RCTs on the body-weight effects of exchanging sugars and non-sugar carbohydrates in the diet is shown in Table 2. The CARMEN trial compared two *ad libitum* low-fat high-carbohydrate diets, which were enriched in simple or complex carbohydrates in 236 overweight subjects in five European countries (27). The diet rich in simple carbohydrates (sugars) reduced body weight over 6 months by 1.6 kg, the diet high in complex carbohydrates (starches) by 2.4 kg. Similar results were found for body fat mass. The differences in body-weight and body fat changes between the diets were not statistically significant. Interpretation of the results of the CARMEN study is complicated by the fact that the high simple and high complex CHO diets not only differed in simple and complex carbohydrate content, but also in fat, protein and total carbohydrate content.

A smaller, but highly controlled, 14-day study by Raben *et al.* compared the impact of *ad libitum* fat-reduced high-sucrose vs. high-starch diets in 20 normal weight or post-obese women in a randomized cross-over design (28). In the high-starch group a significant decrease of body weight and body fat was found (-0.7 and -0.4 kg respectively). No significant body-weight or body fat changes were seen in the high sucrose group (0.2 kg). The difference in weight change between the diets was significant ($P < 0.05$). In this

Table 1 Randomized controlled trials on the effect of low-carbohydrate diets on body weight or body fat in overweight and obese subjects

First author	Year	Subjects	Number	Duration of intervention	Diet composition during intervention [†]	Δ BW I vs. C and/or Δ BF (I–C)	Δ BF I vs. C and/or Δ BF (I–C)	Comments/conclusions
Brehm (81)*	2003	Age > 18 years; BMI 30–35 kg m ⁻²	53	6 months	C: CHO 53%, F 29%, P 18% I: CHO 30%, F 46%, P 23%	-7.2 vs. -3.2 kg ($P < 0.001$)	-4.8 vs. -2.0 kg ($P < 0.01$)	More body weight and fat mass loss on low-carbohydrate high-fat than on high-carbohydrate low-fat diet after 6 months
Foster (82)*	2003	Average age 44 years; average BMI 34 kg m ⁻²	63	12 months	C: CHO 55%, F 30%, P 15% I: CHO ≤ 20 g d ⁻¹ for initial 2 weeks, increase until weight stable Actual intakes not reported	At 6 months: -6.9 vs. -3.2 kg ($P = 0.03$) At 12 months: -7.3 vs. -4.5 kg ($P = 0.27$)		Larger weight loss on low-carbohydrate diet at 6 months; no difference at 12 months
Samaha (83)*	2003	Age > 18 years; BMI > 35 kg m ⁻²	132	6 months	C: CHO 50%, F 34%, P 16% I: CHO 30%, F 52%, P 18%	-5.8 vs. -1.9 kg -3.9 (95% CI -6.3, -1.6)		Larger weight loss on low-carbohydrate diet after 6 months
Stern (84)*	2004			12 months		-5.1 vs. -3.1 kg -2.0 (95% CI -4.9, 1.0)		Follow-up of (83). No difference in weight loss at 12 months
Yancy (85)*	2004	Age 18–65 years; BMI 30–60 kg m ⁻²	120	6 months	C: CHO 52%, F 29%, P 19% I: CHO 8%, F 68%, P 26% (Atkins)	-12.0 vs. -6.5 kg -5.5 kg (95% CI -8.1, -2.9)	-12.9% vs. -6.7% -6.2% (95% CI -8.9, 3.4)	Larger weight loss on low-carbohydrate diet at 6 months
Dansinger (86)*	2005	Average age 49 years; BMI 27–42 kg m ⁻²	80	12 months	C: at 6 (12) months: CHO 46 (45%), F 31 (31%), P 19 (18%); fibre 14 (14) g d ⁻¹ (Weight Watchers) I: at 6 (12) months: CHO 41 (40%), F 39 (38%), P 18 (18%); fibre 13 (15) g d ⁻¹ (Atkins)	At 6 months: -3.2 vs. -3.5 kg (ns) At 12 months: -2.1 vs. -3.0 kg (ns)	WC At 6 months: -3.2 vs. -3.5 cm (ns) At 12 months: -2.5 vs. -3.3 cm (ns)	No long-term differences in weight change between Atkins and Weight Watchers diets
Dyson (18)	2007	Age > 18 years; BMI > 25 kg m ⁻² with or without type 2 diabetes	26	3 months	C: CHO 39%, F 34%, P 20%, energy-restricted (2.1 MJ d ⁻¹ deficit) I: CHO 17%, F 46%, P 31%, <i>ad libitum</i>	-6.9 vs. -2.1 kg ($P = 0.003$)		Larger weight loss on low carbohydrate diet at 3 months; no difference between type 2 diabetics and controls
Swenson (20)	2007	Gastric bypass patients	32	12 months	C: low fat (<35 g d ⁻¹), low protein (50–60 g d ⁻¹) I: South Beach Actual intakes not reported	-17% vs. -14% ($P = 0.15$) (BMI)		Postoperative period. No effect of diet composition on weight change
LeCheminant (19)	2007	Age 19–70 years; BMI > 27 kg m ⁻² before weight loss	55	6 months	C: CHO 55%, F 25%, P 20%; fibre 25 g d ⁻¹ I: CHO 27%, F 48%, P 25%; fibre 14 g d ⁻¹	-0.3 vs. 0.1 kg ($P = 0.87$)	WC 0.4 vs. 2.0 cm (ns)	Weight maintenance after weight loss. No difference in weight loss maintenance between diets

*Included in the meta-analysis by Nordmann *et al.* (17).[†]Reported actual food intake during intervention, unless stated otherwise.

C, control diet; CHO, carbohydrate intake; F, fat intake; I, intervention diet (lower CHO); ns, not significant; P, protein intake as % of energy intake; WC, waist circumference.

Table 2 Randomized controlled trials on the effect of sugar content of the diet on body weight or body fat

First author	Year	Subjects	Number	Duration of intervention	Diet composition during intervention*	ΔBW I vs. C and/or ΔBW (I-C)	ΔBF I vs. C and/or BF (I-C)	Comments/conclusions
Raben (28)	1997	Average age 38 years; average BMI 23 kg m ⁻²	20	14 d	C: CHO 59%, F 28%, P 13%; sucrose 2%; fibre 32 g d ⁻¹ ; <i>ad libitum</i> I: CHO 59%, F 29%, P 13%; sucrose 23%; fibre 20 g d ⁻¹ ; <i>ad libitum</i>	0.2 vs. -0.7 kg (<i>P</i> < 0.05)	No significant difference between diets	Lean and post-obese subjects. Weight loss on high starch diet, no BW change on high-sugar diet
Gatenby (29)	1997	Age 18–50 years; BMI 18–30 kg m ⁻²	19	10 weeks	Sugar intake reduced from 24% to ~19% of energy intake; <i>ad libitum</i>	No change in BW		No control group. No effect of reduction in sugar intake on body weight
Sarris (27)	2000	Age 20–55 years; BMI 26–35 kg m ⁻²	236	6 months	Changes from run-in: C: CHO -1.6%, F 0.8%, P 0.9%; simple CHO -0.9%; fibre -0.1 g d ⁻¹ ; <i>ad libitum</i> I1: CHO 8.4%, F -10.2%, P 1.5%; simple CHO 7.2%; fibre -0.5 g d ⁻¹ ; <i>ad libitum</i> I2: CHO 4.7%, F -7.9%, P 3.6%; simple CHO -3.5%; fibre 1.3 g d ⁻¹ ; <i>ad libitum</i>	I1 vs. I2 vs. C: -0.9 vs. -1.8 vs. 0.8 kg (<i>P</i> = 0.0001); I1 vs. I2 (ns)	I1 vs. I2 vs. C: -1.3 vs. -1.8 vs. 0.6 kg (<i>P</i> = 0.0004); I1 vs. I2 (ns)	No significant difference in weight and fat mass changes between fat-reduced simple and complex carbohydrate-enriched diets
Surwit (31)	1997	Average age 40 years; BW 130–200% of ideal weight	42	6 weeks	Aim: C: CHO 71%, F 11%, P 19%; sucrose 6% of total CHO; fibre 15 g d ⁻¹ ; energy-restricted (4841 kJ d ⁻¹) C: CHO 73%, F 11%, P 19%; sucrose 58% of total CHO; fibre 10 g d ⁻¹ ; energy-restricted (4552 kJ d ⁻¹)	-7.0 vs. -7.4 kg (ns)	-1.3% vs. -1.6% (ns)	Weight loss study. No effect of sugar content of energy-restricted diet on weight loss
West (32)	2001	BW > 7 kg above BMI 25 kg m ⁻²	34	8 weeks	C: CHO 43%, F 37%, P 20%; sucrose 4.6%; energy-restricted (2.5 MJ d ⁻¹ deficit) C: CHO 46%, F 33%, P 21%; sucrose 9.3%; energy-restricted (2.5 MJ d ⁻¹ deficit)	BMI: -1.3 vs. -1.0 kg m ⁻² (ns)		Weight loss study. No effect of sugar content of energy-restricted diet on weight loss

*Reported actual food intake during intervention, unless stated otherwise. BF, body fat; BMI, body mass index; BW, body weight; C, control diet; CHO, carbohydrate intake; F, fat intake; I, intervention diet (higher sugar); ns, not significant; P, protein intake as % of energy intake.

study the macronutrient ratios were similar in the sucrose and starch groups, but there was a significantly higher fibre intake in the starch group, which may have been responsible for the lower energy intake on the high starch diet (28).

In a study by Gatenby *et al.* (29) 49 normal or overweight female subjects were randomized to follow a reduced fat, a reduced sugar (RS) or habitual diet for 10 weeks in a parallel group design. A reported reduction of sugar intake from 24% of energy to ~19% of energy in the RS group was not associated with changes in total carbohydrate intake (suggesting an exchange between sugars and non-sugar carbohydrates), fat intake, protein intake or body weight. Fibre intake was not reported. This study lacks a real control group for the RS group.

The often-cited study by Poppitt *et al.* (30) is a publication on a subgroup of the CARMEN trial and is therefore not included as a separate study here.

In two studies the body-weight effects of high- and low-sugar diets have been compared in the context of an energy-restricted diet (31,32) (Table 2). Surwit *et al.* compared the effects of two energy-restricted diets with high or low sucrose content (58% or 6% energy of total carbohydrate intake) on body-weight loss in 42 overweight and obese women in a parallel group design (31). No differences in weight or fat mass loss were found between the diets. No information on adherence to the diets and macronutrient composition was provided by the investigators. The study by West and de Looy compared two 8-week energy-reduced diets with different sugar contents (5% vs. 10% energy from commercially added sucrose) in 67 overweight adults in a parallel group design (32). A diet creating a 2.5 MJ d⁻¹ negative energy balance was prescribed. Weight loss was significant in both groups with no difference between groups (low sugar -2.2 kg, high sugar -3.0 kg). No significant difference in macronutrient intake was found between groups; fibre intake was not reported.

Conclusions

1. Observational studies show fairly consistent inverse associations between the carbohydrate and sugar content of the diet and body weight and adiposity measures. This is supported by a limited number of RCTs that consistently show lower body weight when fat in the diet is replaced by carbohydrates, in the form of sugars or complex carbohydrates. The evidence can be considered as probable. More pronounced effects on body weight are seen when fat in the diet is replaced by protein.

2. There is insufficient evidence that an exchange of sugar for non-sugar carbohydrates in the context of a fat-reduced *ad libitum* diet or energy-restricted diet results in lower body weights. Additional RCTs, strictly controlling macronutrient ratios and fibre content, are necessary to

definitively assess the effect of exchange of sugars for non-sugar carbohydrates on body-weight control.

Liquid sugar-sweetened beverages

There is increasing concern about a possible relationship between high levels of consumption of sugar-sweetened beverages (SSBs) and obesity, especially in children. The underlying hypothesis is that the sugar calories in liquids have little effect on satiety and therefore easily lead to over-consumption.

A number of reviews on this issue have been published the last 2 years (4,33–35). Terminology and definitions vary among studies, but in most cases all drinks with added sugars, excluding milk and pure fruit juices, are included in the analysis. Mattes concludes, mainly on the basis of cross-sectional and prospective epidemiological studies, that different beverages may have different effects on energy balance, but that most evidence for a positive effect on energy balance is found for clear beverages – including SSBs (34). Malik *et al.* reviewed the literature up till May 2005, including 15 cross-sectional studies, 10 prospective studies and 5 RCTs. The authors concluded that the weight of the epidemiological and experimental evidence indicates that a greater consumption of SSBs is associated with weight gain and obesity (33). Pereira (literature up till 2006, but mostly overlapping with Malik) concludes that the evidence on the role of SSBs in the aetiology of obesity is equivocal owing to unsatisfactory methodology so that current evidence should be regarded as ‘possible’. He expresses the need for high-quality randomized trials to provide the necessary data to obtain ‘convincing’ evidence for the link between SSB intake and obesity risk. The most recent meta-analysis on this topic, including 10 observational studies and 2 RCTs up till 2006, concludes that the association between SSB consumption and BMI is close to zero in children and adolescents (36).

In 2007 additional prospective analyses on the effect of SSB consumption on body weight or adiposity in several cohorts have been published. A study in over 2000 young Canadian children showed that regular consumers of soft drinks between meals at ages 2.5–4.5 years had an overweight prevalence at age 4.5 years of 14.5%, whereas only 6.9% of non-consumers was overweight at that age (37). In contrast, no evidence for an association between SSB consumption at age 5 years ($n = 521$) or 7 years ($n = 682$) and fatness at age 9 years was found in a cohort of British children (38). In a study in 244 German adolescents between 9 and 18 years an increase in SSB consumption was associated with an increase in BMI-SDS in girls but not in boys over 5 years of follow-up (39).

The effect of soft drink consumption on components of the metabolic syndrome were analysed in over 6000 middle-aged participants the Framingham Heart Study

(40). Consumption of ≥ 1 soft drink per day was associated with a higher prevalence of obesity (OR 1.31; 95% CI 1.02, 1.68) and increased waist circumference (OR 1.30; 95% CI 1.09, 1.56).

These studies add to the body of epidemiological literature suggestive of, although not fully consistent, a positive association between BMI and SSB consumption.

SSBs vs. non-sugar containing beverages

An overview of RCTs on SSB consumption and body weight is shown in Table 3. There are only two studies that directly compared the body-weight effects of SSBs and non-sugar-containing beverages (41,42). The study by Tordoff and Alleva (42) was included in the reviews by Pereira (35) and Malik *et al.* (33), but not the study by Reid *et al.* (41). In the first study, supplementation with aspartame-sweetened beverages or HFCS-sweetened beverages (1135 g d⁻¹) for 3 weeks each was compared with no beverage in a randomized cross-over study (42). During the no beverage control period subjects tended to lose some weight, but this effect was not significant; during the aspartame period body weight did not change, whereas it increased significantly during the HFCS period. The other study, a randomized controlled intervention study with a parallel group design, studied the effect of 4 weeks' SSB supplementation, providing 1800 kJ d⁻¹, compared with aspartame-sweetened beverage supplementation in 133 lean, adult women eating a low-fat diet (41). Non-SSB carbohydrate intake, fat intake and protein intake were lower in the SSB group than in the aspartame group. A non-significant trend for weight gain was reported in the SSB group only. Primary aim of this study was to study long-term dietary compensation. SSB supplementation reduced carbohydrate, fat and protein intake, in contrast to aspartame-sweetened beverages. However, the reduction did not fully compensate for the SSB-associated caloric intake so that total energy intake was increased by 1000 kJ d⁻¹ in the SSB group.

Blackburn *et al.* (43) and Raben *et al.* (44) compared the effects of sugars and artificial sweeteners in the diet (as drinks as well as solid foods) in the context of a weight loss programme of 16 weeks or an *ad libitum* diet of 10 weeks respectively (Table 3). In the weight loss study there was no difference in weight loss between the two groups (aspartame group -9.9 kg vs. sugar-group -9.8 kg) (43). In the *ad libitum* study subjects were asked to consume a minimum amount of either sucrose-sweetened or artificially sweetened drinks and foods per day. Seventy per cent of sucrose came from drinks, 30% from solid foods. Sucrose supplements provided 3.4 MJ d⁻¹, sweetener supplements 1.0 MJ d⁻¹. Body weight increased in the sucrose group and it decreased in the aspartame group, resulting in a 2.6 kg

higher body weight in the sucrose group ($P < 0.001$) after 10 weeks (44).

Liquid vs. solid sugars

Anderson argues that the associations between SSBs and obesity must be viewed as circumstantial because biological plausibility and short-term experimental studies do not support cause and effect conclusions (45). This conclusion is mainly based on the fact that there is insufficient evidence that sugars in solid form stimulate intake regulatory mechanisms and suppress food intake more than those in commonly consumed beverages.

Only one RCT has directly compared the body-weight effects of liquid and solid sugar intake (46). In a cross-over study 15 lean subjects received 1.88 MJ d⁻¹ of jelly beans or caffeine-free sugar-sweetened soda for 4 weeks each. In both groups the increased sugar intake was associated with a significantly reduced intake of fat and protein. Non-sugar carbohydrate intake was reduced in the jelly bean group only. Body weight increased significantly in the soda group (0.5 kg, $P < 0.05$) and did not change significantly in the jelly bean group (0.3 kg). The difference between the groups was not statistically significant. The authors conclude from this study that dietary compensatory responses to energy-yielding beverages are less precise than those of iso-energetic solid loads (46). The study has been criticized because most of the sodas were consumed as part of a meal, whereas the jelly beans were consumed in between meals. Two studies compared the acute satiating effects of solid or liquid sugar ingestion in lean and overweight subjects (47,48). Almiron-Roig *et al.* (47) compared equal-energy 1.25 MJ preloads of regular cola and fat-free raspberry cookies. Lavin *et al.* (48) compared sucrose-containing pastilles, jelly or drinks, which were ingested in 10, 5 and 2 min respectively. Energy intake from a test lunch did not differ between preloads in the study by Almiron-Roig *et al.* (47), but was lower after chewing the pastilles than after the drink in the study by Lavin *et al.* (48).

Conclusions

1. Epidemiological studies, cross-sectional as well as cohort studies, mostly show an association between SSB consumption and body weight, suggestive of a possible relationship between SSB consumption and risk of overweight.

2. A limited number of RCTs that have directly compared SSBs with artificially sweetened drinks show a tendency for body-weight gain with SSB supplementation, but differences with the control group were not statistically significant. More RCTs of sufficient size and duration are clearly required in this area to support the data from epidemiological studies.

Table 3 Randomized controlled trials on the effects of aspartame- and sugar-sweetened beverages or foods and of liquid and solid sugar on body weight and body fat

First author	Year	Subjects	Number	Duration of intervention	Diet composition during intervention*	Δ BW 1 vs. C and/or Δ BW (I-C)	Δ BF 1 vs. C and/or Δ BF (I-C)	Comments/conclusion
Tordoff (42)	1990	Not specified	30	3 weeks	I1 (aspartame): CHO 43%, F 42%, P 15%, sugars 20% I2 (HFCS, 2.2 MJ d ⁻¹): CHO 50%, F 28%, P 23%, sugars 37% Control period without intervention	I2-I1: 0.7 kg (women); 0.9 kg (men)		Cross-over; statistics only for comparison with non-soda control. HFCS-sweetened beverage consumption increased BW significantly, aspartame-sweetened beverage consumption did not affect BW compared with the non-supplemented control period
Reid (41)	2007	Female, age 29–55 years; BMI 18.5–24.9 kg m ⁻²	133	4 weeks	C (aspartame): CHO 47%, F 36%, P 16% I (sucrose, 1.8 MJ d ⁻¹): CHO 58%, F 28%, P 13%	I: Δ BMI 0.06 kg m ⁻² C: Δ BMI -0.24 kg m ⁻² (P < 0.05)		Trend for sucrose group to gain weight
Blackburn (43)	1997	Age 20–60 years; BW 140–225% of ideal BW	128	16 weeks active weight loss and 1 year weight maintenance; follow-up at 3 years	At 16 weeks (1 year): C (no-aspartame): CHO 49 (49)%, F 28 (31)%, P 23 (19)%, sucrose 8 (10)%, energy intake 5.1 (6.0) MJ d ⁻¹ I (aspartame): CHO 49 (47)%, F 27 (34)%, P 24 (19)%, sucrose 6 (8)%, energy intake 5.3 (6.1) MJ d ⁻¹	At 16 weeks: -9.9 kg vs. -9.8 kg; no difference between groups At 1 year: 5.4 vs. 2.6 kg weight regain At 3 years: 9.4 vs. 5.4 kg weight regain (P < 0.05)		Weight loss study. Significantly better long-term weight maintenance in aspartame group
Raben (44)	2002	Age 20–50 years; BMI 25–30 kg m ⁻²	41	10 weeks	C (artificial sweeteners): CHO 45%, F 35%, P 15%, sucrose 4% I (sucrose): CHO 57%, F 29%, P 11%, sucrose 24%	1.6 vs. -1.0 kg (P < 0.001)	1.3 vs. -0.3 kg (P < 0.001)	Significantly more body weight gain on high sucrose than on artificial sweeteners
DiMeglio (46)	2000	Average age 23 years; average BMI 22 kg m ⁻²	15	4 weeks	C (solid): CHO 225 g d ⁻¹ , F 56 g d ⁻¹ , P 72 g d ⁻¹ ; sugar 95 g d ⁻¹ (excl jelly beans); jelly beans, 1.9 MJ d ⁻¹ I (liquid): CHO 242 g d ⁻¹ , F 85 g d ⁻¹ , P 91 g d ⁻¹ ; sugar 78 g d ⁻¹ (excl SSB); SSB, 1.9 MJ d ⁻¹	0.3 vs. 0.5 kg	0.2 vs. 0.4 kg	Cross-over study. BW gain from baseline significant in SSB group only; no statistics for comparison between jelly bean and SSB group

*Reported actual food intake during intervention, unless stated otherwise. BF, body fat; BMI, body mass index; BW, body weight; C, control diet; CHO, carbohydrate intake; F, fat intake; HFCS, high fructose corn syrup; I, intervention diet (higher sugar or liquid sugar); P, protein intake as % of energy intake; SSB, sugar-sweetened beverage.

3. There is no support for the hypothesis that liquid sugar has a detrimental effect on body weight compared with solid forms of sugar from RCTs. Evidence from a small number of acute studies with respect to satiety and energy intake compensation is equivocal. There is a clear need for more RCTs of sufficient size and duration in this area.

Glycaemic index and glycaemic load

The GI refers to the blood-glucose-raising potential of carbohydrate foods. The GI of a given food is defined as the two-hour incremental area under the blood glucose response curve (IAUC) following the intake of a portion of the food that contains 50 g of carbohydrates, expressed as percent of the two-hour IAUC following the intake of 50 g of CHO from a reference food (glucose or white bread) consumed by the same person on a different day (49). Factors that influence the glycaemic response are the nature of the mono- and disaccharides (ratio between glucose, fructose, galactose), the nature of the starch (e.g. ratio between amylose and amylopectin), cooking and food processing (e.g. degree of starch gelatinization, particle size, cellular structure) and the presence of other food components (e.g. fat and protein, dietary fibre, organic acids). GI values of foods have been published by Foster-Powell *et al.* (50). The foods in this table are mainly of American and Australian origin and GI values from different sources and different types and numbers of subjects have been entered in the table. A recent inter-laboratory study revealed considerable variation in reported GI values of the same foods (51). Foods with a GI ≤ 55 are classified as low GI, whereas foods with a GI ≥ 70 are classified as high GI foods.

The main dietary sources of glycaemic sugars are fruit and vegetables (sucrose, glucose and fructose), milk and dairy (lactose and galactose) and added sugars (sucrose, glucose and fructose) (52). According to the Foster-Powell table, the GI of fructose is 19 ± 2 , of maltose (consisting of 2 glucose molecules) 105 ± 12 , of sucrose (consisting of 1 glucose and 1 fructose molecule) 68 ± 5 , and of lactose (consisting of 1 glucose and 1 galactose molecule) 46 ± 2 . No data are reported on the GI of galactose. Because some sugars (glucose, maltose) are high in GI and others low (fructose, lactose), the contribution of sugars to the GI of the diet may vary and, depending on their nature, sugars may be part of a high as well as a low-GI diet.

Because the glycaemic response to food ingestion also depends on the total amount of carbohydrates ingested, the concept of GL has been introduced. The GI of a diet is calculated by summing up the products of the total amount of digestible carbohydrate and the GI of each food, divided by the total amount of digestible carbohydrate intake. The dietary GL is calculated in the same way as the GI, but by dividing by 100 instead of dividing by the total carbohy-

drate intake. GL therefore reflects the total glycaemic burden of the diet by taking both the GIs and the amounts of the different types of carbohydrates in the diet into account.

Although increased consumption of low-GI foods has been advocated for some time for the prevention and treatment of obesity (53–55), the role of GI and GL in body-weight regulation is still a much debated and controversial issue (56–59). The discussions are complicated by problems with GI value estimates, the fact that GL can be manipulated by changing GI but also by changing total carbohydrate intake independent of changes in GI, bias by associated changes in other macronutrients, and the fact that low GI foods are often higher in fibre.

Epidemiological studies

In his review Gaesser concluded that epidemiological studies suggest that higher-GL diets may be beneficial for weight control and that there is no clear effect of higher-GI diets on BMI, but that these findings should be interpreted with great caution owing to methodological issues associated with this type of studies. For instance, data from the Inter99 study demonstrate that the outcome of such studies is significantly affected by underreporting (60). Three additional studies that were not included in this review have been published since. One showed a positive association between GI and GL and BMI (61), whereas the other two found no association with body weight or adiposity (61–63). Interestingly, Davis *et al.* (62) reported a positive association between sugar intake and adiposity in Latino children in the absence of an association with GL or GI. In this population, the sugar intake accounted for nearly 50% of total carbohydrate intake.

A prospective study in a cohort of 376 Danish adults showed that high-GI diets may lead to body-weight gain and body fat gain in women, especially in those that are sedentary. In men no associations were found (64).

Randomized controlled trials

In 2007 a systematic Cochrane review was published on RCTs with the primary aim to study the effectiveness of low-GI or low-GL diets for weight loss in healthy overweight and obese subjects, published until July 2006 (65). Six studies were included in the review (66–71). The weighted mean difference in weight loss (high minus low GI/GL) in the four studies that reported absolute weight changes was -1.09 kg (95% CI $-0.18, -1.99$) in favour of the low-GI/GL diets (66,69–71), in fat mass the difference was -1.13 kg (95% CI $-0.38, -1.89$) (66,67,69,71). Further details on the design and outcome of these studies can be found in Table 4. The conclusion of the review was that overweight or obese people on low-GI diets lost more

Table 4 Randomized controlled trials on the effect of glycaemic index and glycaemic load of the diet on body weight or body fat in healthy overweight and obese subjects

First author	Year	Subjects	Number	Duration of intervention	Diet composition†	ΔBW (l vs. C) and/or ΔBW (l-C)	ΔBF (l vs. C) and/or ΔBF (l-C)	Comments/conclusion
Slabber (70)*	1994	Average age 35 years; average BMI 35 kg m ⁻²	30	12 weeks	C: CHO 50%, F 30%, P 20%; energy-restricted; high insulinemic; no information on GI or fibre; actual intakes not reported I: CHO 50%, F 30%, P 20%; energy-restricted; low insulinemic; no information on GI or fibre; actual intakes not reported	-2.94 (95% CI -5.35, -0.53)		Diet that invokes low insulin response reduces weight in obese hyper-insulinemic women
Bouché (66)*	2002	Average age 46 years; average BMI 28 kg m ⁻²	11	5 weeks	C: CHO 42%, F 37%, P 18%; GI = 71; fibre 19 g; <i>ad libitum</i> I: CHO 39%, F 38%, P 20%; GI = 41; fibre 31 g; <i>ad libitum</i>	-0.5 vs. -0.02 kg (P < 0.05)		Cross-over study. Low-GI diet decreases fat mass
Ebbeling (67)*	2003	Age 13-21 years; BMI > 95th centile	16	6 months intervention, follow-up at 12 months	C: CHO 55%, F 28%, P 18%; GI = 56; GL = 77 g 4.2 MJ ⁻¹ ; fibre = 9 g 4.2 MJ ⁻¹ ; energy-restricted I: CHO 51%, F 31%, P 19%; GI = 53; GL = 68 g 4.2 MJ ⁻¹ ; fibre = 10 g 4.2 MJ ⁻¹ ; <i>ad libitum</i>	At 12 months: BMI -1.3 vs. 0.7 kg m ⁻² (P = 0.02)		Larger BMI and fat mass reduction with GI/GL-reduced diet
Sloth (71)*	2004	Age 21-41 years; BMI 25-30 kg m ⁻²	45	10 weeks	C: CHO 57%, F 22%, P 17%; fibre = 34 g d ⁻¹ ; <i>ad libitum</i> I: CHO 57%, F 23%, P 17%; fibre = 31 g d ⁻¹ ; <i>ad libitum</i> ; estimated GI difference between C and I: 24	-1.9 vs. -1.3 kg (P = 0.31) -0.60 (95% CI -1.74, 0.54)		Difference in GI without difference in GL between diets. No difference in body-weight change between high- and low-GI diet
Ebbeling (68)*	2005	Age 18-35 years; BMI > 27 kg m ⁻²	23	6 months intervention, follow-up at 12 months	At 6 months: C: CHO 59%, F 23%, P 19%; GI = 53; GL = 78 g 4.2 MJ ⁻¹ ; fibre 13 g; energy-restricted I: CHO 47%, F 33%, P 21%; GI = 46; GL = 54 g 4.2 MJ ⁻¹ ; fibre 15 g; <i>ad libitum</i>	At 6 months: -8.4 vs. -7.8 kg (ns) At 12 months: -7.8 vs. -6.1 kg (ns)		No difference in body weight change between high-GI/GL and low-GI/GL diets
McMillan-Price (69)*	2006	Age 18-40 years; BMI > 25 kg m ⁻²	64	12 weeks	C (diet 1): CHO 60%, F 19%, P 18%; GI = 70; GL = 129 g d ⁻¹ ; fibre 25 g; energy-restricted I (diet 2): CHO 56%; F 22%, P 19%; GI = 45; GL = 89 g d ⁻¹ ; fibre 30 g; energy-restricted	-3.7 vs. -4.8 kg -1.09 (95% CI -3.26, 0.66)		Diet 1 vs. diet 2. No difference in weight loss, but significantly larger fat mass reduction on GI/GL-reduced diet
Ebbeling (78)	2007	Age 18-35 years; obese	73	6 months intervention, follow-up at 12 and 18 months	At 6 months: C: CHO 55%, F 23%, P 21%; GI = 57; GL = 70 g 4.2 MJ ⁻¹ ; fibre 12 g; <i>ad libitum</i> I: CHO 40%, F 38%, P 22%; GI = 45; GL = 37 g 4.2 MJ ⁻¹ ; fibre 13 g; <i>ad libitum</i>	At 6 months: -4.5 vs. -3.8 kg (ns) No significant differences at 12 and 18 months	At 6 months: -1.3 kg vs. -1.4 kg (ns) No significant difference at 18 months	More pronounced loss of BW and BF in subjects with high-insulin response at 30 min of oral glucose tolerance test on low-GI/GL diet

Table 4 Continued

First author	Year	Subjects	Number	Duration of intervention	Diet composition [†]	ΔBW (I vs. C) and/or ΔBW (I-C)	ΔBF (I vs. C) and/or ΔBF (I-C)	Comments/conclusion
de Rougemont (77)	2007	Age 20-60 years; BMI 25-30 kg m ⁻²	38	5 weeks	C: CHO 44%, F 38%, P 18%; GI = 66; GL = 16.5 g d ⁻¹ ; fibre 18 g; <i>ad libitum</i> I: CHO 43%, F 38%, P 20%; GI = 46; GL = 11.3 g d ⁻¹ ; fibre 26 g; <i>ad libitum</i>	-1.1 vs. -0.2 kg (P = 0.04)	-0.7 vs. -0.2% (P = 0.50)	More weight and fat loss on GI/GL-reduced diet
Sichieri (80)	2007	Age 25-45 years; BMI 23-30 kg m ⁻²	203	18 months	C: CHO 61%, F 27%; GI = 83; GL = 300 g d ⁻¹ ; fibre 38 g; energy-restricted I: CHO 58%, F 28%; GI = 42; GL = 114 g d ⁻¹ ; fibre 30 g; energy-restricted	At 6 months: -0.87 vs. -1.27 kg At 12 months: -1.00 vs. -1.25 kg At 18 months: -0.41 vs. -0.26 kg (all ns)		No differences in weight changes between high- or low-GI/GL diets
Bellisle (75)	2007	Age >18 years; BMI > 25 kg m ⁻²	65	12 weeks	C: Weight Watchers POINTS with high GI choices; no information on actual food intake I: Weight Watchers POINTS with low GI choices; no information on actual food intake	-4.0 vs. -4.5 kg (P = 0.68)	-5.5 vs. -6.1 mm waist (P < 0.88)	Number of low GI products selected higher in low-GI group; frequency not different. No effect of stimulating consumption of low GI products on weight or fat mass
Aston (74)	2008	Age 34-65 years; BMI > 25 kg m ⁻²	19	12 weeks	C: CHO 48%, F 34%, P 18%; GI = 64; GL = 139 g d ⁻¹ ; fibre 16 g; <i>ad libitum</i> I: CHO 51%, F 32%, P 17%; GI = 56; GL = 134 g d ⁻¹ ; fibre 16 g; <i>ad libitum</i>	-0.1 (-1.1, 0.9) (P = 0.8)	0.22 (95% CI -0.50, 0.94) (P = 0.9)	Cross-over study. Small difference in GI and GL between diets. No difference in body weight or fat mass changes between high- or low-GI diets
Das (76)	2007	Age 20-42 years; BMI 25-30 kg m ⁻²	34	12 months	C: CHO 60%, F 20%, P 20%; GI = 86; GL = 12.1 g d ⁻¹ ; fibre 15 g; energy-restricted I: CHO 40%, F 30%, P 30%; GI = 52; GL = 8.2 g d ⁻¹ ; fibre 15 g; energy-restricted	-10.4 vs. -9.1% (6 months)		6 months food provided. No difference in weight changes between high and low-GI diets
Maki (79)	2007	Age 18-65 years; waist circumference: ≥87 cm (women), ≥90 cm (men)	84	12 weeks weight loss, followed by 24 weeks weight loss maintenance	At week 12: C: CHO 46%, F 37%, P 19%; GI = 51, GL = 126 g d ⁻¹ ; fibre 18 g d ⁻¹ ; energy-restricted I: CHO 32%, F 42%, P 26%; GI = 46, GL = 7.3 g d ⁻¹ ; fibre 17 g d ⁻¹ ; <i>ad libitum</i> At week 36 diets were similar	At week 12: -2.5 vs. -4.9 kg (P = 0.002) At week 36: -2.6 vs. -4.5 kg (P = 0.085)	At week 12: -0.9 vs. -1.9 kg (P = 0.016) At week 36: -1.3 kg vs. -2.0 kg (P = 0.333)	Larger short-term weight and fat mass loss on energy-restricted lower-GI diet

[†]Included in the meta-analysis by Thomas *et al.* (65).

[‡]Reported actual food intake during intervention, unless stated otherwise.

BF, body fat; BMI, body mass index; BW, body weight; C, control diet; CHO, carbohydrate intake; F, fat intake; GI, glycaemic index; GL, glycaemic load; I, intervention diet (lower GI/GL); ns, not significant; P, protein intake as % of energy intake.

weight than those on control diets and that lowering of the GL of the diet appears to be an effective method of promoting weight loss (65).

Livesey *et al.* published a meta-analysis on controlled GI intervention studies published until January 2005. He also included studies in subjects with type 1 or type 2 diabetes, impaired glucose tolerance, hyperlipidemia and coronary heart disease risk (72,73). This meta-analysis included 19 studies and showed a statistically significant trend for a fall in body weight with a reduction of GL or GI. This trend was apparent in the studies where food intake was *ad libitum* or only under limited control, not in those where food intake was controlled.

Since July 2006 seven additional RCTs on GI/GL and body weight in healthy overweight or obese subjects have been published (74–80). Details of these studies can be found in Table 4. Weight loss difference (high–low GI/GL) varied between 0.5 kg (75) and –1.9 kg (79) and was statistically significant in one study only (77). These studies confirm the results of the two meta-analyses in that if there is an effect of low-GI/GL diets on body weight it is likely to be small and of limited practical and clinical importance.

Van Dam and Seidell concluded from their review of the literature on low-GI and low-GL diets that the evidence is too limited to warrant specific recommendations with respect to the application of these concepts for the prevention of obesity (4).

Independent role of glycaemic index

It is difficult to tease out the specific role of GI in body-weight control from the studies in Table 4. Only the study by Sloth *et al.* (71) had similar macronutrient compositions and fibre intakes in the two intervention groups. The estimated GI difference was 24 between the groups, but body-weight and fat mass differences (–0.6 kg over 10 weeks) between groups were not statistically significant. The study by Aston *et al.* (74) had only small differences in macronutrient composition and fibre intakes between the groups, but the GI difference between the groups (8 points) was also small. Body weight (–0.1 kg) and body fat (0.2 kg) differences over 12 weeks between groups were not statistically significant.

In conclusion, there are currently not enough carefully designed randomized controlled studies that allow definitive conclusions about the specific role of the GI of the diet in body-weight control. Published studies so far do not support an important role for GI (71,74).

Role of glycaemic load

The meta-analysis by Livesey *et al.* showed a statistically significant trend for a fall in body weight with a reduction of GL (72). This trend was apparent in the studies where

food intake was *ad libitum* or only under limited control, not in those where food intake was controlled. The independent contribution of total carbohydrate intake, GI or fibre intake in the effect of GL was not analysed.

Most of the studies in Table 4 that were published in 2006 and 2007, which were not included in the Livesey paper, support the trend for a lower body weight on lower-GL diets (68,69,76–79), although only in the study by de Rougemont *et al.* (77) the difference was statistically significant. On the other hand, two other studies, including a large Brazilian study with over 200 subjects, showed an opposite trend (75,80).

Livesey *et al.* conclude in their meta-analysis that a reduction of dietary GL tends to lower body weight, but that the effect is modest and is most consistent with a GL reduction of at least 42 g d^{–1} (72). Based on a descriptive review of a similar selection of studies, Van Dam and Seidell, on the other hand, conclude that studies that have directly compared low- and high-GL diets do not consistently support the hypothesis that a low-GL diet supports weight loss (4).

Conclusions

1. There is currently no evidence that an *ad libitum* diet with a low GI causes a lower body weight than a diet with a high GI when total carbohydrate intake is not different. However, there is a clear need for more well-designed RCTs with GI differences between intervention groups of different magnitudes to investigate a potential dose–response relationship.

2. There is some evidence from a fair number of mostly RCTs that *ad libitum* and moderately energy-restricted diets with a low GL are associated with modest body-weight loss compared with diets with a high GL. Whether this is a specific effect of GL or of total amount of carbohydrate needs to be elucidated.

Conflict of Interest Statement

MvB is recipient of research grants and honoraria as speaker from a number of Dutch and international companies and has no conflict of interest related to sugar.

AA is advisor or member of advisory boards for a number of food and pharmaceutical producers etc.: Aria, European Almond Advisory Board, Communications and Scientific Advisory Board of The Global Dairy Platform, Johnson & Johnson Research Institute, 7TM Pharma, Novo, NeuroSearch, Pfizer, Novartis, Basic Research, Unilever, Butterflies, Merck, and Reuters Insight, GSK, and recipient of honoraria as speaker for a wide range of Danish and international concerns. AA has no conflict of interests related to sugar.

References

1. Saris WH. Sugars, energy metabolism, and body weight control. *Am J Clin Nutr* 2003; **78**: 850S–857S.
2. Cummings JH, Stephen AM. Carbohydrate terminology and classification. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S5–S18.
3. Forshee RA, Storey ML, Allison DB, Glinsmann WH, Hein GL, Lineback DR, Miller SA, Nicklas TA, Weaver GA, White JS. A critical examination of the evidence relating high fructose corn syrup and weight gain. *Crit Rev Food Sci Nutr* 2007; **47**: 561–582.
4. Van Dam R, Seidell J. Carbohydrate intake and obesity. *Eur J Clin Nutr* 2007; **61**: S75–S99.
5. Gaesser GA. Carbohydrate quantity and quality in relation to body mass index. *J Am Diet Assoc* 2007; **107**: 1768–1780.
6. Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO. The role of low-fat diets in body weight control: a meta-analysis of ad libitum dietary intervention studies. *Int J Obes Relat Metab Disord* 2000; **24**: 1545–1552.
7. Bray GA, Popkin BM. Dietary fat intake does affect obesity! *Am J Clin Nutr* 1998; **68**: 1157–1173.
8. Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM. Effects of the national cholesterol education program's step i and step ii dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr* 1999; **69**: 632–646.
9. Howard BV, Manson JE, Stefanick ML, Beresford SA, Frank G, Jones B, Rodabough RJ, Snetselaar L, Thomson C, Tinker L, Vitolins M, Prentice R. Low-fat dietary pattern and weight change over 7 years: the women's health initiative dietary modification trial. *JAMA* 2006; **295**: 39–49.
10. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.
11. Lindstrom J, Eriksson JG, Valle TT, Aunola S, Cepaitis Z, Hakumaki M, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Martikkala V, Moltchanov V, Rastas M, Salminen V, Sundvall J, Uusitupa M, Tuomilehto J. Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the finnish diabetes prevention study: results from a randomized clinical trial. *J Am Soc Nephrol* 2003; **14**: S108–113.
12. Westerterp-Plantenga M, Luscombe-Marsh N, Lejeune M, Diepvens K, Nieuwenhuizen A, Engelen M, Deutz N, Azzout-Marniche D, Tome D, Westerterp K. Dietary protein, metabolism, and body-weight regulation: dose-response effects. *Int J Obes* 2006; **30**: S16–S23.
13. Brinkworth GD, Noakes M, Keogh JB, Luscombe ND, Wittert GA, Clifton PM. Long-term effects of a high-protein, low-carbohydrate diet on weight control and cardiovascular risk markers in obese hyperinsulinemic subjects. *Int J Obes Relat Metab Disord* 2004; **28**: 661–670.
14. Brinkworth GD, Noakes M, Parker B, Foster P, Clifton PM. Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with type 2 diabetes: one-year follow-up of a randomised trial. *Diabetologia* 2004; **47**: 1677–1686.
15. Clifton PM, Keogh JB, Noakes M. Long-term effects of a high-protein weight-loss diet. *Am J Clin Nutr* 2008; **87**: 23–29.
16. Due A, Toubro S, Skov AR, Astrup A. Effect of normal-fat diets, either medium or high in protein, on body weight in overweight subjects: a randomised 1-year trial. *Int J Obes Relat Metab Disord* 2004; **28**: 1283–1290.
17. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS Jr, Brehm BJ, Bucher HC. Effects of low-carbohydrate vs. low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166**: 285–293.
18. Dyson PA, Beatty S, Matthews DR. A low-carbohydrate diet is more effective in reducing body weight than healthy eating in both diabetic and non-diabetic subjects. *Diabet Med* 2007; **24**: 1430–1435.
19. Lecheminant JD, Gibson CA, Sullivan DK, Hall S, Washburn R, Vernon MC, Curry C, Stewart E, Westman EC, Donnelly JE. Comparison of a low carbohydrate and low fat diet for weight maintenance in overweight or obese adults enrolled in a clinical weight management program. *Nutr J* 2007; **6**: 36.
20. Swenson BR, Saalwachter Schulman A, Edwards MJ, Gross MP, Hedrick TL, Weltman AL, Northrup CJ, Schirmer BD, Sawyer RG. The effect of a low-carbohydrate, high-protein diet on post laparoscopic gastric bypass weight loss: a prospective randomized trial. *J Surg Res* 2007; **142**: 308–313.
21. Astrup A, Meinert Larsen T, Harper A. Atkins and other low-carbohydrate diets: hoax or an effective tool for weight loss? *Lancet* 2004; **364**: 897–899.
22. Gibson S, Neate D. Sugar intake, soft drink consumption and body weight among british children: further analysis of national diet and nutrition survey data with adjustment for under-reporting and physical activity. *Int J Food Sci Nutr* 2007; **58**: 445–460.
23. Gibson SA. Are diets high in non-milk extrinsic sugars conducive to obesity? An analysis from the dietary and nutritional survey of British adults. *J Hum Nutr Diet* 2007; **20**: 229–238.
24. Astrup A, Raben A. Carbohydrate and obesity. *Int J Obes Relat Metab Disord* 1995; **19**(Suppl. 5): S27–S37.
25. Hill JO, Prentice AM. Sugar and body weight regulation. *Am J Clin Nutr* 1995; **62**: 264S–273S. discussion 273S–274S.
26. Rodearmel SJ, Wyatt HR, Stroebele N, Smith SM, Ogden LG, Hill JO. Small changes in dietary sugar and physical activity as an approach to preventing excessive weight gain: the America on the Move Family Study. *Pediatrics* 2007; **120**: e869–e879.
27. Saris WH, Astrup A, Prentice AM, Zunft HJ, Formiguera X, Verboeket-van de Venne WP, Raben A, Poppitt SD, Seppelt B, Johnston S, Vasilaras TH, Keogh GF. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs. complex carbohydrates on body weight and blood lipids: the Carmen study. The carbohydrate ratio management in European national diets. *Int J Obes Relat Metab Disord* 2000; **24**: 1310–1318.
28. Raben A, Macdonald I, Astrup A. Replacement of dietary fat by sucrose or starch: effects on 14 d ad libitum energy intake, energy expenditure and body weight in formerly obese and never-obese subjects. *Int J Obes Relat Metab Disord* 1997; **21**: 846–859.
29. Gatenby SJ, Aaron JI, Jack VA, Mela DJ. Extended use of foods modified in fat and sugar content: nutritional implications in a free-living female population. *Am J Clin Nutr* 1997; **65**: 1867–1873.
30. Poppitt SD, Keogh GF, Prentice AM, Williams DE, Sonnemans HM, Valk EE, Robinson E, Wareham NJ. Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. *Am J Clin Nutr* 2002; **75**: 11–20.
31. Surwit RS, Feinglos MN, McCaskill CC, Clay SL, Babyak MA, Brownlow BS, Plaisted CS, Lin PH. Metabolic and behavioral effects of a high-sucrose diet during weight loss. *Am J Clin Nutr* 1997; **65**: 908–915.

32. West JA, de Looy AE. Weight loss in overweight subjects following low-sucrose or sucrose-containing diets. *Int J Obes Relat Metab Disord* 2001; **25**: 1122–1128.
33. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr* 2006; **84**: 274–288.
34. Mattes R. Fluid calories and energy balance: the good, the bad, and the uncertain. *Physiol Behav* 2006; **89**: 66–70.
35. Pereira M. The possible role of sugar-sweetened beverages in obesity etiology: a review of the evidence. *Int J Obes* 2006; **30**: S28–S36.
36. Forshee RA, Anderson PA, Storey ML. Sugar-sweetened beverages and body mass index in children and adolescents: a meta-analysis. *Am J Clin Nutr* 2008; **87**: 1662–1671.
37. Dubois L, Farmer A, Girard M, Peterson K. Regular sugar-sweetened beverage consumption between meals increases risk of overweight among preschool-aged children. *J Am Diet Assoc* 2007; **107**: 924–934 (Discussion 934–935).
38. Johnson L, Mander AP, Jones LR, Emmett PM, Jebb SA. Is sugar-sweetened beverage consumption associated with increased fatness in children? *Nutrition* 2007; **23**: 557–563.
39. Libuda L, Alexy U, Sichert-Hellert W, Stehle P, Karaolis-Danckert N, Buyken AE, Kersting M. Pattern of beverage consumption and long-term association with body-weight status in German adolescents – results from the Donald study. *Br J Nutr* 2008; **16**: 1–9.
40. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* 2007; **116**: 480–488.
41. Reid M, Hammersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: effects of supplementary sucrose drinks over a 4-week period. *Br J Nutr* 2007; **97**: 193–203.
42. Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. *Am J Clin Nutr* 1990; **51**: 963–969.
43. Blackburn GL, Kanders BS, Lavin PT, Keller SD, Whatley J. The effect of aspartame as part of a multidisciplinary weight-control program on short- and long-term control of body weight. *Am J Clin Nutr* 1997; **65**: 409–418.
44. Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 weeks of supplementation in overweight subjects. *Am J Clin Nutr* 2002; **76**: 721–729.
45. Anderson G. Sugar-containing beverages and post-prandial satiety and food intake. *Int J Obes* 2006; **30**: S52–S59.
46. DiMeglio D, Mattes R. Liquid versus solid carbohydrate: effects on food intake and body weight. *Int J Obes* 2000; **24**: 794–800.
47. Almiron-Roig E, Flores S, Drewnowski A. No difference in satiety or in subsequent energy intakes between a beverage and a solid food. *Physiol Behav* 2004; **82**: 671–677.
48. Lavin J, French S, Ruxton C, Read N. An investigation on the role of oro-sensory stimulation in sugar satiety. *Int J Obes* 2002; **26**: 384–388.
49. FAO/WHO. Carbohydrates in human nutrition. Report of a joint fao/who expert consultation. *FAO Food Nutr Pap* 1998; **66**: 1–140.
50. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* 2002; **76**: 5–56.
51. Wolever TM, Brand-Miller JC, Abernethy J, Astrup A, Atkinson F, Axelsen M, Bjorck I, Brighenti F, Brown R, Brynes A, Casiraghi MC, Cazaubiel M, Dahlqvist L, Delport E, Denyer GS, Erba D, Frost G, Granfeldt Y, Hampton S, Hart VA, Hatonen KA, Henry CJ, Hertzler S, Hull S, Jerling J, Johnston KL, Lightowler H, Mann N, Morgan L, Panlasigui LN, Pelkman C, Perry T, Pfeiffer AF, Pieters M, Dan Ramdath D, Ramsingh RT, Robert SD, Robinson C, Sarkkinen E, Scazzina F, Sison DC, Sloth B, Staniforth J, Tapola N, Valsta LM, Verkooijen I, Weickert MO, Weseler AR, Wilkie P, Zhang J. Measuring the glycemic index of foods: interlaboratory study. *Am J Clin Nutr* 2008; **87**: 247S–257S.
52. Englyst KN, Liu S, Englyst HN. Nutritional characterization and measurement of dietary carbohydrates. *Eur J Clin Nutr* 2007; **61**(Suppl. 1): S19–S39.
53. Brand-Miller JC. Glycemic load and chronic disease. *Nutr Rev* 2003; **61**: S49–S55.
54. Liu S. Lowering dietary glycemic load for weight control and cardiovascular health: a matter of quality. *Arch Intern Med* 2006; **166**: 1438–1439.
55. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* 2002; **287**: 2414–2423.
56. McMillan-Price J, Brand-Miller J. Low-glycaemic index diets and body weight regulation. *Int J Obes* 2006; **30**: S40–S46.
57. Pawlak DB, Ebbeling CB, Ludwig DS. Should obese patients be counselled to follow a low-glycaemic index diet? Yes. *Obes Rev* 2002; **3**: 235–243.
58. Raben A. Should obese patients be counselled to follow a low-glycaemic index diet? No. *Obes Rev* 2002; **3**: 245–256.
59. Sloth B, Astrup A. Low glycemic index diets and body weight. *Int J Obes* 2006; **30**: S47–S51.
60. Lau C, Toft U, Tetens I, Richelsen B, Jorgensen T, Borch-Johnsen K, Glumer C. Association between dietary glycemic index, glycemic load, and body mass index in the inter99 study: is under-reporting a problem? *Am J Clin Nutr* 2006; **84**: 641–645.
61. Murakami K, Sasaki S, Okubo H, Takahashi Y, Hosoi Y, Itabashi M. Dietary fiber intake, dietary glycemic index and load, and body mass index: a cross-sectional study of 3931 Japanese women aged 18–20 years. *Eur J Clin Nutr* 2007; **61**: 986–995.
62. Davis JN, Alexander KE, Ventura EE, Kelly LA, Lane CJ, Byrd-Williams CE, Toledo-Corral CM, Roberts CK, Spruijt-Metz D, Weigensberg MJ, Goran MI. Associations of dietary sugar and glycemic index with adiposity and insulin dynamics in overweight latino youth. *Am J Clin Nutr* 2007; **86**: 1331–1338.
63. Milton JE, Briche B, Brown IJ, Hickson M, Robertson CE, Frost GS. Relationship of glycaemic index with cardiovascular risk factors: analysis of the national diet and nutrition survey for people aged 65 and older. *Public Health Nutr* 2007; **10**: 1321–1335.
64. Hare-Bruun H, Flint A, Heitmann BL. Glycemic index and glycemic load in relation to changes in body weight, body fat distribution, and body composition in adult danes. *Am J Clin Nutr* 2006; **84**: 871–879 (Quiz 952–953).
65. Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev* 2007; July 18 (3): CD005105.
66. Bouché C, Rizkalla SW, Luo J, Vidal H, Veronese A, Pacher N, Fouquet C, Lang V, Slama G. Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men. *Diabetes Care* 2002; **25**: 822–828.
67. Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A reduced-glycemic load diet in the treatment of adolescent obesity. *Arch Pediatr Adolesc Med* 2003; **157**: 773–779.

68. Ebbeling CB, Leidig MM, Sinclair KB, Seger-Shippee LG, Feldman HA, Ludwig DS. Effects of an ad libitum low-glycemic load diet on cardiovascular disease risk factors in obese young adults. *Am J Clin Nutr* 2005; **81**: 976–982.
69. McMillan-Price J, Petocz P, Atkinson F, O'Neill K, Samman S, Steinbeck K, Caterson I, Brand-Miller J. Comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: a randomized controlled trial. *Arch Intern Med* 2006; **166**: 1466–1475.
70. Slabber M, Barnard HC, Kuyl JM, Dannhauser A, Schall R. Effects of a low-insulin-response, energy-restricted diet on weight loss and plasma insulin concentrations in hyperinsulinemic obese females. *Am J Clin Nutr* 1994; **60**: 48–53.
71. Sloth B, Krog-Mikkelsen I, Flint A, Tetens I, Bjorck I, Vinoy S, Elmstahl H, Astrup A, Lang V, Raben A. No difference in body weight decrease between a low-glycemic-index and a high-glycemic-index diet but reduced ldl cholesterol after 10-week ad libitum intake of the low-glycemic-index diet. *Am J Clin Nutr* 2004; **80**: 337–347.
72. Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr* 2008; **87**: 258S–268S.
73. Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health a systematic review and meta-analysis: the database, study characteristics, and macronutrient intakes. *Am J Clin Nutr* 2008; **87**: 223S–236S.
74. Aston LM, Stokes CS, Jebb SA. No effect of a diet with a reduced glycaemic index on satiety, energy intake and body weight in overweight and obese women. *Int J Obes (Lond)* 2008; **32**: 160–165.
75. Bellisle F, Dalix AM, De Assis MA, Kupek E, Gerwig U, Slama G, Oppert JM. Motivational effects of 12-week moderately restrictive diets with or without special attention to the glycaemic index of foods. *Br J Nutr* 2007; **97**: 790–798.
76. Das SK, Gilhooly CH, Golden JK, Pittas AG, Fuss PJ, Cheatham RA, Tyler S, Tsay M, McCrory MA, Lichtenstein AH, Dallal GE, Dutta C, Bhapkar MV, Delany JP, Saltzman E, Roberts SB. Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial. *Am J Clin Nutr* 2007; **85**: 1023–1030.
77. de Rougemont A, Normand S, Nazare JA, Skilton MR, Sothier M, Vinoy S, Laville M. Beneficial effects of a 5-week low-glycaemic index regimen on weight control and cardiovascular risk factors in overweight non-diabetic subjects. *Br J Nutr* 2007; **98**: 1288–1298.
78. Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low-glycemic load vs. low-fat diet in obese young adults: a randomized trial. *JAMA* 2007; **297**: 2092–2102.
79. Maki KC, Rains TM, Kaden VN, Raneri KR, Davidson MH. Effects of a reduced-glycemic-load diet on body weight, body composition, and cardiovascular disease risk markers in overweight and obese adults. *Am J Clin Nutr* 2007; **85**: 724–734.
80. Sichieri R, Moura AS, Genelhu V, Hu F, Willett WC. An 18-mo randomized trial of a low-glycemic-index diet and weight change in Brazilian women. *Am J Clin Nutr* 2007; **86**: 707–713.
81. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metab* 2003; **88**: 1617–1623.
82. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, Klein S. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003; **348**: 2082–2090.
83. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams T, Williams M, Gracely EJ, Stern L. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003; **348**: 2074–2081.
84. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 2004; **140**: 778–785.
85. Yancy WS Jr, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med* 2004; **140**: 769–777.
86. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* 2005; **293**: 43–53.

Diabetes, insulin resistance and sugars

M. Laville^{1,2,3} and J.-A. Nazare^{1,2,3}

¹Centre de Recherche en Nutrition Humaine Rhône-Alpes, Univ de Lyon, Lyon, France;
²INSERM, INRA, Univ Lyon, Lyon, France;
³Hospices Civils de Lyon, Lyon, France

Received 30 October 2008; revised 28 November 2008; accepted 28 November 2008

Address for correspondence: M Laville, Centre de Recherche en Nutrition Humaine Rhône-Alpes (CRNH-RA), Bâtiment 1, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon cedex 03, France. E-mail: martine.laville@chu-lyon.fr

Summary

Insulin resistance is associated with type 2 diabetes, hypertension and cardiovascular disease and the dietary factors involved in these metabolic disorders are still misunderstood. In animal studies, sugars, particularly sucrose and fructose, have been shown to decrease insulin sensitivity, with potential association with an induced hypertriglyceridemia. But in humans, the effects of sugars on insulin sensitivity are still debated.

The present work first gives an overview of the metabolic pathways that could be implicated in the development of insulin resistance by sugars. Then, a review of the studies (intervention, prospective and cross-sectional) on the relationship between sugars, insulin resistance and diabetes is made in order to determine the level of proof concerning the association of sugars consumption and diabetes.

All these studies failed to demonstrate an obvious relationship between the intake of total simple carbohydrates and glycaemic control or risk to develop a type 2 diabetes and particularly specific evidence is missing in terms of sucrose effect on diabetes.

Concerning fructose, there are still discrepancies between studies' conclusions about the long-term deleterious effect on diabetes development. But its effect on lipogenesis and triglyceridemia has to be taken into account, considering the growing use of fructose in food industry and sugar-sweetened drinks.

Keywords: Diabetes, insulin resistance, sugars.

obesity reviews (2009) **10** (Suppl. 1), 24–33

Introduction

'Sugars' is a common term to describe mono- and disaccharides and represent an important part of the total caloric intake. Glucose, fructose and sucrose are the most consumed sugars in diet. In the general population, a recent important change in the dietary habits is the increase of the consumption of fructose, owing to the increased intake of sucrose and fructose corn syrup, sweetener commonly used in food industry, especially in the USA. Animal studies have shown an effect of high-sucrose and high-fructose diet in decreasing insulin sensitivity, with potential association with an induced hypertriglyceridemia (1).

Current dietary recommendations for diabetes management (type 1 or type 2) do not contain precise guidelines about the intake of sugars except that they should be substituted on a caloric basis for others carbohydrates, focus

being more on overall caloric amount. In type 1 diabetes, the restriction of carbohydrates intake was the basis of diabetes medical nutrition therapy before insulin therapy. Now postprandial hyperglycaemia is mainly controlled by acting on pre-meal insulin doses on the basis of carbohydrates counting. The use of carbohydrates has been brought back into favour on an isocaloric basis as fat intake has been limited because of the impact on lipid metabolism and cardiovascular risks. In type 2 diabetes, the attention is more on carbohydrate caloric content and on glycaemic index (GI).

The limitation of sugars intake has been justified by several observations: their contribution to the increase of energy density of food, their association with weight gain and over-consumption, etc. It has been suggested that increased consumption of refined and simple carbohydrates may promote the development of diabetes. But for instance, if fructose has been shown to increase plasma triglyceride

concentrations, its effect on insulin sensitivity is still debated.

The World Health Organization, the Food and Agriculture Organization and the American Heart Association recommended a restriction of free sugars intake in order to prevent diabetes and obesity, based on potential detrimental effects on metabolism: they suggested free sugars intake to be no more than 10% of calories. But it is still in debate whether sufficient evidence exists to justify the restriction of sugars intake in terms of prevention of obesity and diabetes.

We will first make a reminder of the metabolism of sugars and focus on the metabolic pathways which could be involved in the development of insulin resistance. Then we will give an overview of the studies on the relationship between sugars, insulin resistance and diabetes, in order to determine the level of proof concerning the association of sugars consumption and diabetes.

Sugars metabolism and effect on glucose and lipid metabolism

Absorption and digestion

Human studies on gastric emptying have shown that the intestinal delivery of fructose solutions is twice quicker than with glucose solutions (2). Absorption of fructose is a facilitated diffusion mechanism, when glucose absorption is an active energy-dependant mechanism (3). Intestinal fructose absorption has been shown to be a linear process, on the contrary of the glucose one, which remains quicker. This difference could be explained by the different characteristics of their transporter (4,5). The absorption of sucrose needs a prior hydrolysis in fructose and glucose. *In vitro* studies have shown that glucose from sucrose is absorbed faster than free glucose. Moreover, it has been shown that, on the contrary of glucose, fructose absorption is incomplete (6). But there is a large inter-individual variability for the absorption capacity.

After ingestion, the sucrose arrives in portal vein in the form of fructose and glucose and the organism used these two monosaccharides. Unlike fructose, an oral glucose load is captured by extra-splanchnic tissues in majority.

The first step of the glucose use by tissues is the transport from extracellular environment to intracellular one, by co-transporters Na⁺/glucose or facilitated diffusion transporters (GLUT). The GLUT on the hepatocitary membrane favours net glucose capture in the postprandial state and net delivery in the post-absorptive state. There are five facilitated diffusion glucose transporters: GLUT1, GLUT2, GLUT3, GLUT4, GLUT5, whose expression in the different tissues is shown in Table 1. Fructose-specific transporter is GLUT5, but also GLUT2.

Table 1 Tissues expression of glucose transporters

SGLT1	Apical pole of enterocyte
Cotransporteur Na ⁺ /glucose	Kidney
GLUT1	Placenta, brain, kidney, colon, leucocytes, intestin
GLUT2	Liver, leucocytes, baso-lateral membrane of enterocyte, kidney
GLUT3	Most tissues including brain, placenta, kidney
GLUT4	Skeletal and cardiac muscle, adipose tissue
GLUT5	Skeletal muscle, adipose tissue, brain, apical pole of enterocyte

The metabolic pathways of fructose and glucose are shown on Fig. 1. Fructose is metabolized in liver, kidney and intestine with three enzymes: fructokinase (FK), l'aldolase B et la triokinase (7). After an oral load, fructose is almost exclusively metabolized in liver, where the limiting step is the FK.

Muscle metabolic use of fructose is considered to be very limited and adipose tissue is supposed to play a more important role.

In tissues that have the suitable specific metabolic pathway, fructose is a very active substrate on glucose metabolism. In liver for example, fructolysis is far quicker than glycolysis, fructose is a better precursor for glucose than lactate and for glycogen than glucose (7).

Glucose and insulin responses after an oral load of fructose, glucose and sucrose

Glucose and insulin responses to a fructose oral load are lower than after an equivalent glucose load. Moreover, increasing doses of fructose or glucose have different effects on insulin response (8,9). For a load of 0.5 and 1 g kg⁻¹ of glucose, insulin response is proportional to the load but glucose response is similar. But with fructose, insulin and glucose responses are the same. This difference could be explained by a very weak effect of fructose on the rate of appearance of total glucose in plasma (8). After a glucose load, the increase of the rate of appearance of total glucose is mainly due to the appearance of exogenous glucose in plasma, while endogenous glucose production is strongly inhibited by hyperglycaemia and insulinemia (9,10). In response so a fructose load, the appearance of glucose comes from the transformation of fructose in glucose in liver.

The glucose response to a load of 30 g of sucrose is different to the response to a load of 30 g fructose +30 g glucose (8,9,11). After the sucrose load, the glycaemic peak appears earlier at 30 min than after a glucose load, but the amplitude is the same. This could be caused by a fast

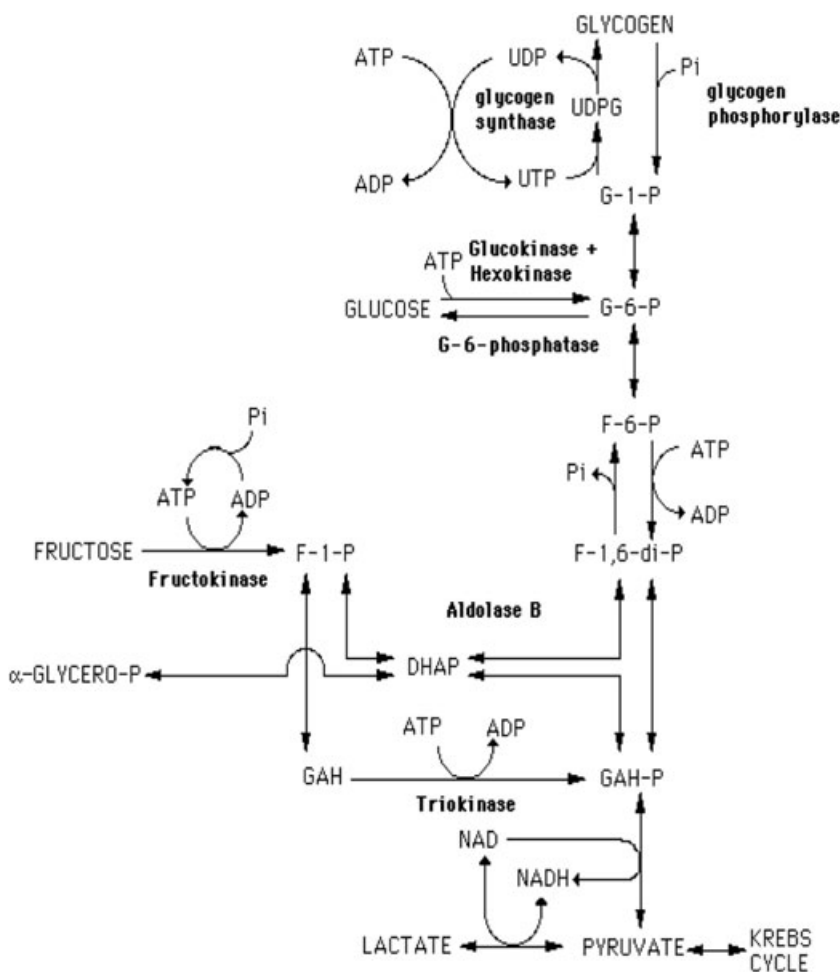


Figure 1 Biochemical pathways of fructose and glucose metabolism.

transformation of the fructose from sucrose in glucose, which is added to the glucose from sucrose. This hypothesis should be confirmed by isotopic analysis but is already reinforced by a non-different insulinemic peak between sucrose and glucose. In fact, fructose is not insulin activating *per se*, but glucose formed from this fructose could have had an additive activating effect on insulin secretion.

So, fructose, glucose and sucrose are the most commonly ingested carbohydrates. Fructose and glucose bioavailabilities are different and could be explained by three factors:

- fructose after capture is almost all metabolized by liver whereas the main part of an oral glucose load is metabolized in peripheral tissues;
- fructose is metabolized in liver by a specific pathway whose first enzymatic step is catalysed by fructokinase, whose velocity is far superior than glucokinase or hexokinase;
- fructose metabolism is mainly insulin-independent where glucose metabolism is insulin dependant.

All in all, the effect of sucrose on glucose and insulin responses is close to the effect of glucose. But its oxidative fate seems to be closer to the fructose one. After a load of 1 g kg^{-1} of fructose, net carbohydrate oxidation is faster during the first hour than after a similar glucose load. After 6 h, 100% of the fructose load ingested has been oxidated whereas with glucose load some glucose remained available for glycogen storage.

After the ingestion of sucrose, carbohydrate oxidation is strongly stimulated like with fructose (11). Kinetics is similar to the fructose one, indicating that the fructose part of the sucrose could determine the carbohydrate oxidation speed of sucrose.

Effect on lipid metabolism and lipogenesis

The effects of fructose on lipid metabolism are mainly observed in liver. The relation between fructose metabolism and lipid metabolism is shown on Fig. 2.

In liver, the effect of fructose on lipid metabolism is through the production of dihydroxyacetone-phosphate

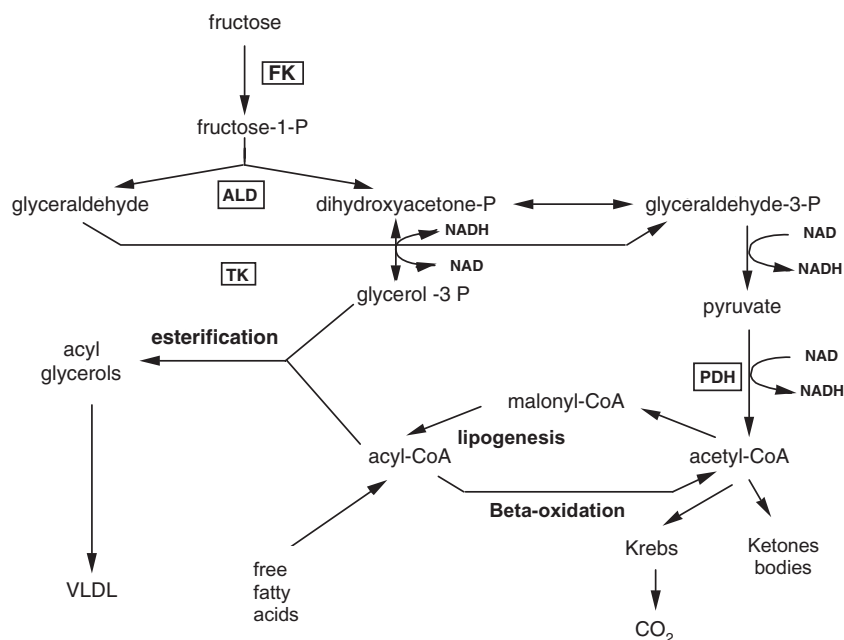


Figure 2 Relation between fructose and lipid metabolism.

(DHAP) and pyruvate (12,13). The fructolysis supplies carbons to glycerol and to the acyl part of the triglyceride molecule. A lipogenic effect of fructose has not been shown with fructose alone and may be observed in combination with glucose and insulin. But fructose itself has an effect on the metabolic fate of non-esterified fatty acids (NEFA). It stimulates the re-esterification of NEFA and has an additive effect with insulin. An anti-ketogenic effect of fructose has been shown and could be due to the re-esterification of NEFA induced by fructose at the expense of their oxidation. But at supra-physiologic concentrations, fructose is ketogenic.

Fructose inhibits as strongly as glucose the NEFA even if the insulin secretory effect of fructose is weak, owing to the effect on intra-hepatic re-esterification of NEFA.

Fructose strongly stimulates *de novo* lipogenesis. Studies have shown that hepatic lipogenesis is minor and that in adipose tissue it is also weak. There are a synthesis and a re-esterification of NEFA in liver and the kinetics of this *de novo* lipogenesis is parallel to the concentration of triglycerides after a fructose load (8).

After a fructose load, *de novo* lipogenesis is stimulated but on other hand, after a similar load of glucose, lipogenesis is not. The increase of triglycerides induced by sucrose results from the effects of:

- fructose: stimulation of lipogenesis and re-esterification of NEFA;
- glucose: re-esterification of NEFA by stimulation of insulin.

The possible metabolic consequences of the stimulation of *de novo* lipogenesis after sucrose ingestion come from

the alteration of the fatty acids composition of triglycerides in very-low-density lipoprotein (VLDL). In fact, it results in an increase of the concentration of saturated fatty acids and in a decrease of their hydrolysis by lipoprotein lipase, which increases triglycerides concentration by reducing VLDL clearance. Moreover, it also results in a larger part of saturated fatty acids which are incorporated in membrane phospholipids. And this change in membrane composition could alter the ability of adipose tissue or skeletal tissue to catch glucose (14). It has been shown in several insulin resistant populations, that there is an inverse relationship between saturated fatty acids concentration in membrane or muscular triglycerides and insulin sensitivity (15).

Only fructose (and sucrose containing fructose) has a lipogenic effect in liver and could potentially modify fatty acids' balance in VLDL and induce harmful secondary effects like hypertriglyceridemia or insulin resistance.

The nature of mono- and disaccharides plays a role in the lipogenic effect but *de novo* lipogenesis remains a minor pathway in humans. The lipogenic effect of sucrose is not bigger than that of glucose. Fructose is more controversial: it could increase triglycerides but also cholesterol, blood pressure (8). Hallfrish found this increase in triglycerides only in baseline hyper-insulinemic men associated with an increase in cholesterol and LDL cholesterol (16). Discrepancies between studies remain concerning a deleterious effect of a diet rich in fructose on cholesterol and/or triglycerides, notably between men and women. But still, these studies suggested that high intake of fructose are not justified in population at risk: men, insulin resistant and/or hyper-insulinic subjects, postmenopausal women, type 2 diabetics, hypertensive or subjects with polymetabolic syndrome.

It has been proven that a diet rich in carbohydrates or in high-GI or simple carbohydrates and especially fructose increases fasting and postprandial triglycerides. It is a long-lasting phenomenon with a low-level threshold. The increase of triglycerides is moderate except in subjects at risk (men, postmenopausal women, hyper-insulinemia, glucose intolerance).

Sugars, insulin resistance and diabetes

Assessing the association between sugars and insulin resistance and the pathogenesis of diabetes in human studies is difficult. The heterogeneity in studies' design and the problems induced by the composition of the diets (change of more than one dietary variable in the diet) could lead to discrepancies in results. Moreover, the assessment of insulin resistance or insulin sensitivity has not always been conducted using specific methods and was most of the time based on fasting and/or postprandial metabolic profile (Table 2).

Data have been classified in four groups in descending order of level of proofs: intervention studies, cohort-type prospective studies, cross-sectional studies. A note has been given to each study corresponding to its level of proof: very high A, high B, average C, weak D.

Intervention studies

Several studies have been made to compare the effect of sucrose or fructose instead of starch (8 studies) or the effect of sucrose instead of fructose (2 studies), with 7 studies concerning type 1 diabetes and 15 concerning type 2 diabetes. One study compared two *ad libitum* low-fat high-carbohydrate diets enriched in simple or complex carbohydrates.

Two studies (A and B) have shown a deleterious effect of sucrose (20–30%) on insulin resistance, when the diet contained up to 30% of total calories in the form of sucrose instead of starch (17,18). In Reiser study (18) twenty-four carbohydrate-sensitive adults consumed diets containing 5%, 18% and 33% of calories as sucrose for 6 weeks each in a cross-over design and serum insulin was significantly higher at 1 h after the 18% sucrose diet and at 0.5, 1, 2 and 3 h after the 33% sucrose diet, both compared with the 5% sucrose diet. Glucose response was also significantly greater after the 18% and 33% sucrose diets than after the 5% sucrose diet.

But three other studies (2A + 1B) did not find any effect (19–21). In Bantle *et al.* study (19), the short-term (8 d) replacement of carbohydrates source with sucrose (23% of energy intake) did not have significant effect on glycaemic control in 12 type 1 and 12 type 2 diabetic subjects. In the study of Peterson, 12 type 1 and 11 type 2 diabetic subjects took part in a randomized cross-over

study and ate 2 high-fibre/low-carbohydrate diets with one containing 45 g of sucrose instead of 45 g of starch. There were no significant differences on glucose and insulin profile.

In another recent study classified B (22), 9 overweight subjects received a high-sucrose (increase of 50 g), high-monounsaturated fat isocaloric diet for 24 d and this increase of sucrose intake (13% of total energy intake) was not related to a decrease in insulin sensitivity or in glycaemic control. In the same way, in a randomized cross-over study (B) with twice 6-week intervention, a high-sucrose eucaloric weight-maintaining diet was not associated with detrimental effects on insulin sensitivity or glycaemic profile (23).

The effect is even less clear for fructose. A study classified A (24) indicated a deleterious effect on insulin resistance (5-week diet containing 15% of total calories in the form of fructose instead of starch) in 12 men with abnormally high insulin responses to a sucrose load and 12 healthy men: the 15% fructose diet resulted in significantly higher insulin and glucose responses than consumption of the other two diets. Two other studies classified A showed a beneficial effect of high-fructose diets (10–30% of carbohydrate calories) on insulin resistance (19,25). In Koivisto study, type 2 diabetic subjects ate placebo or fructose (20% of carbohydrate calories, 45–65 g per day) administered evenly during day meals and their insulin sensitivity was increased (34%) during the fructose diet. In this randomized, double-blind, placebo-controlled cross-over design, insulin sensitivity was assessed using euglycaemic clamping in a group of type 2 diabetic subjects (7 of 10 treated with oral hypoglycaemic drugs) (25).

The effect of fructose instead of sucrose has also been tested: one study B on seven type 2 diabetic subjects showed a beneficial effect (10%) of a 2-week high-fructose diet on insulin resistance (estimated by postprandial glucose concentration) (26). But another study A did not show any effect: in this 3-month diet, six type 2 diabetic subjects replaced 13% of their calories intake as fructose instead of sucrose incorporated to meals and this substitution did not have deleterious effect on insulin resistance (estimated by a hyper-insulinemic euglycaemic clamp and sugar tolerance test) (27). Following 4 weeks of daily intake of fructose (18% of calorie intake), Le showed an increase in triglycerides but no change in insulin sensitivity in healthy subjects (28).

In the CARMEN trial (Carbohydrate Ratio Management in European National diets), the effects of altering the ratio of fat to carbohydrate on body weight, blood lipid and other metabolic parameters were assessed using a low-fat high-complex carbohydrate diet vs. a low-fat high-simple carbohydrate diet (29). No effect of either dietary intervention was observed on fasting glucose and insulin concentrations.

Table 2 Summary of intervention, prospective and cross-sectional trials assessing the association between sugars, insulin resistance and diabetes

First author	Year	Subjects	Number	Duration of intervention	Diet composition during intervention	Results	Comments
<i>Intervention studies</i>							
Reiser (17)	1979	Healthy or hypertriglyceridemic	19	Twice 6 weeks (cross-over)	30% of the calories as either sucrose or wheat starch C: CHO 43%, F 42%, P 15%	Fasting glucose and insulin response and insulin : glucose ratio higher after sucrose diet	10% of calories eaten at breakfast 90% of calories eaten at dinner
Reiser (18)	1981	Carbohydrate-sensitive (hyper-insulinemic)	24	3 times 6 weeks (cross-over)	2%, 15% or 30% of the calories as sucrose at the expense of wheat starch. C: CHO 44%, F 42%, P 14%	Fasting and postprandial insulin and glucose increased with sucrose content Higher glucose response after 18 and 33% sucrose diet	25% of calories eaten at breakfast 75% of calories eaten at dinner
Bantle (19)	1986	Type 1 or type 2 diabetic	24	Twice 1 week (cross-over)	21% or 23% of the calories as sucrose or fructose respectively at the expense of starch (bread and potatoes)	No effect of sucrose compared with starch on glucose control (fasting and postprandial) Fructose increased glycaemic control	
Bantle (20)	1993	Type 2 diabetic	12	Twice 4 weeks (cross-over)	19% of the calories as sucrose at the expense of starch (bread or potatoes)	No effect of sucrose compared with starch on glycaemic control (fasting glucose)	
Peterson (21)	1986	Type 1 or type 2 diabetic	23	Twice 6 weeks (cross-over)	Isocaloric diets, high in fibre and low in fat. 45 g of complex carbohydrate was replaced by 45 g of sucrose taken at mealtimes in one diet	No differences in mean daily plasma glucose levels or diurnal glucose profiles	
Brynes (22)	2007	Overweight type 2 diabetic	9	24 d	50 g increase in sucrose (13% of total energy intake) in combination with a high monounsaturated fat isocaloric diet	No change in insulin sensitivity (short insulin tolerance test) or glycaemic control	
Black (23)	2006	Healthy	13	Twice 6 weeks (cross-over)	High- vs. low-sucrose (25% vs. 10% of total energy intake), eucaloric, weight-maintaining diets	No changes in glycaemic profile, no detrimental effect on insulin sensitivity (2-step euglycaemic-hyper-insulinemic clamp)	
Hallfrisch (24)	1983	12 hyper-insulinemic 12 normal	24	3 times 5 weeks (cross-over)	0%, 7.5% or 15% of the calories as fructose C: CHO 43%, F 42%, P 15%	Increased fasting glucose, insulin and glucose responses	
Koivisto (25)	1993	Type 2 diabetic	10	4 weeks	Fructose intake as 20% of carbohydrate calories (45-65 g day) vs. placebo, administered evenly during 4 meals/snacks per day	Increased insulin sensitivity (34%) during fructose diet (euglycaemic clamp)	
Crapo (26)	1986	Type 2 diabetic	7	2 weeks	Fructose as a sweetener	Beneficial reduction of insulin resistance (10%) when assessed by postprandial glucose concentration	
Thorburn (27)	1990	Type 2 diabetic	6	3 months	13% of calories as fructose in place of sucrose	No effect of fructose substitution on glucose and insulin responses	
Le (28)	2006	Healthy	7	4 weeks	1.5 g kg ⁻¹ d ⁻¹ fructose = 18% of total calories	Increase in triglycerides but no change in insulin sensitivity	

Table 2 Continued

First author	Year	Subjects	Number	Duration of intervention	Diet composition during intervention	Results	Comments
Saris (29)	2000	Healthy overweight	236	6 months	4 experimental groups: a 'no intervention' group, a control group with average national intake, a low-fat high simple carbohydrates group and a low-fat high complex carbohydrates group	No effect of either dietary intervention on fasting glucose and insulin concentrations	No detailed for specific sugars
<i>Prospective and cross-sectional studies</i>							
Janket (35)	2003	Women aged 45 years and older	39 345	–	Validated semi-quantitative food frequency questionnaire (sugar intake, including sucrose, glucose, fructose and lactose)	No effect of total simple carbohydrate, nor of fructose, sucrose, glucose or lactose alone on diabetes incidence	
Meyer (30)	2000	low women initially free of diabetes	35 988	6 years (1141 incident cases of diabetes reported)	Validated food frequency questionnaire (food sources of carbohydrates, subtypes of carbohydrates)	No link with lactose or maltose consumption but a growing risk (30%) to develop diabetes when consuming >25.8 g d ⁻¹ of glucose or 30 g d ⁻¹ of fructose Reduced risk for women consuming >51 g d ⁻¹ of sucrose	
Salmeron (31)	1997	Men free of diabetes or cardiovascular disease	42 759	6 years (523 incident cases of diabetes reported)	Validated semi-quantitative food frequency questionnaire (total sugars)	No significant effect of total sugars intake on type 2 diabetes risk	
Montonen (34)	2007	Men and women initially free of diabetes	4 304	12 years (177 incident cases of diabetes reported)	Validated semi-quantitative food frequency questionnaire (content of different sugars in food)	Combined intake of fructose and glucose and sweetened drinks but not sucrose, lactose or maltose was associated with risk of type 2 diabetes	
Schulze (36)	2004	Women initially free of diabetes	91 249	8 years (741 incident cases of diabetes reported)	Validated food frequency questionnaire (detailed for sugar-sweetened drinks, fruit juices, diet soft drinks, fruit punch)	Increased relative risk of diabetes (1.83) for women consuming 1 or more sugar-sweetened soft drink per day compared with <1 per month	
Buyken (37)	2001	Type 1 diabetic	2 810	–	3-day dietary record (total carbohydrates, fibre)	lower dietary glycaemic index related to lower HbA1c concentrations	No detailed for specific sugars
Wolever (38)	1999	Type 1 diabetic	272	–	3-day dietary record (starch, simple sugars (mono- and disaccharides), oligosaccharides, dietary fibre and glycaemic index)	No significant correlation between HbA1c or insulin dose and sugars, total carbohydrates or glycaemic index	
Sevak (39)	1994	South Asian and white initially free of diabetes	173	–	7-day weighed-food dietary assessments (total carbohydrates, sucrose, starch)	Insulin concentration 2-h post-glucose correlated with carbohydrate intake, stronger correlation for sucrose than for starch	

All these data suggest that the replacement in intervention studies of a large part of the caloric intake by starch, sucrose or fructose does not have an obvious deleterious effect in the short term on insulin resistance and on glycaemic control in healthy or diabetic subjects. Data obtained in one type of subjects (healthy or diabetic) should be interpreted cautiously before a potential extrapolation to the general population.

Prospective studies

Concerning type 2 diabetes, six prospective studies have been made on large cohort (between 4000 and 85 000 subjects), mainly from USA: Women's Health study (30), Iowa Women's Health study (31), Health Professional Follow-up Study (32), Nurses' Health Study (33,34), and one in Finland (35). They lasted between 5 and 16 years. Among these studies, three have been classified A representing a very high level of proof (32–34); the three others have been classified B, with a high level of proof (30,31,35).

Two studies presented the effect of simple carbohydrates. In the Women Health Study, the authors did not find any effect of the total simple carbohydrates, nor of sucrose, fructose, glucose or lactose alone (30). Meyer, in the Iowa Women's Health Study (31), did not find a link with lactose or maltose consumption but found a growing risk (30%) to develop a type 2 diabetes in women consuming more than 25.8 g d⁻¹ of glucose and a growing risk of 27% in women consuming more than 30 g d⁻¹ of fructose. In another way, women consuming more than 51 g d⁻¹ of sucrose had a reduced risk (19%) to develop a type 2 diabetes compared with women consuming less than 31 g d⁻¹.

In the Nurses' Health study, the influence of total sugars was studied and there was no significative effect of total sugars intake on the risk of type 2 diabetes (33).

Moreover, data from the Nurses' health study II on a prospective cohort of more than 91 000 women free of diabetes at the beginning of the follow-up showed that women consuming 1 or more sugar-sweetened soft drink a day had a relative risk of diabetes of 1.83 ($P < 0.001$) compared with those consuming less than one per month. This may be because of the excessive calories providing, as well as the large part of rapidly absorbable sugars found in these products. It has to be noticed that sugar-sweetened soft drinks contain large amount of high-fructose corn syrup. (Fruit juices consumption was not associated with diabetes, suggesting a different effect of naturally occurring sugars and added sugars, or a counterbalancing effect of others fruit components like vitamins, fibres, minerals etc.) (36).

In another cohort of 4300 men and women initially free of diabetes, a 12-year follow-up with food consumption and sugars intake report showed that fructose, glucose and

sweetened beverages were associated with risk of type 2 diabetes but not sucrose, lactose or maltose (36).

According to these prospective data, it seems that there is a trend for a deleterious effect of fructose and glucose on diabetes risk in the long term, but not sufficient evidence to conclude about sucrose, maltose or lactose. Still, discrepancies between studies show further investigations are needed in order to precise the long-term independent effects of specific sugars intake in terms of insulin resistance.

Cross-sectional studies

Few cross-sectional studies could be used in order to illustrate the discussion, as most of the time, they give precise GI of the diet and carbohydrates intake but lack of details concerning the composition in sugars. Food-frequency questionnaires, frequently used, give a limited accuracy in estimated detailed food intake. Moreover, the difference between added or natural (in fruits or dairy products) simple carbohydrates is rarely reported.

First, several cross-sectional studies have analysed the relationship between carbohydrates consumption and glycaemia or glycaemic control, in type 1 diabetes (37,38). No relationship has been observed between the intake of carbohydrates (simple and total) and glycaemia and/or glycated haemoglobin (HbA1c). But in Buyken's study, a lower dietary GI was related to lower HbA1c concentrations.

The study of South Asian and white men on 173 subjects (classified A) used 7-day weighed-food dietary assessments and fasting and 2-h after glucose load insulin concentration to estimate the link between type 2 diabetes incidence and dietary factors (39). A significant positive correlation was found between 2-h insulin concentration after a glucose load and carbohydrate intake, with a stronger correlation for sucrose than for starch.

Conclusion

All these studies do not demonstrate an obvious relationship between the intake of total simple carbohydrates and glycaemic control or risk to develop type 2 diabetes, and specific evidence is particularly missing in terms of sucrose effect on diabetes.

Conflicting results could come from the heterogeneity in the kind of studied subjects all through the different studies (diabetic, hyper-insulinemic, hypertriglyceridemic, healthy, etc.) (1). There is limited supporting evidence for recommendations on sugars intake which could be easily extended to the general population, as high intake of sugars could be more deleterious for certain groups of subjects. There are still discrepancies between studies' conclusions about the long-term deleterious effect of fructose on diabetes development. Recently, high fructose intake has been

associated by many studies as a risk factor for metabolic syndrome and diabetes. But it is mainly based on biochemical observations, as fructose is supposed to induce insulin resistance through a metabolic dyslipidemia caused by increased *de novo* lipogenesis and triglycerides synthesis. In fact, even if there is a short-term potential favourable effect of fructose intake on postprandial hyperglycaemia, it could also elevate plasma lipids, triglycerides and this could be responsible for long-term deleterious effects. That is why it seems of prime importance to take this in account in order to advice the growing use of fructose and fructose syrup in food industry and sugar-sweetened drinks.

A potential dietary adverse effect of sucrose may appear for high sucrose intakes (>30% of caloric intake), but 30% is far higher than the average sucrose intake.

We could noticed that the American Diabetic Association expert panel, after the analysis of 22 studies, concluded that sucrose does not alter glycaemic control in diabetic subjects when ingested in isocaloric quantities, in fact it should be consumed in substitution for other carbohydrates. Also, the ADA recommends that the total amount of carbohydrate in meals or snacks is more important than the source or type.

Still, more studies are needed in order to determine the impact of strict restriction of simple carbohydrates intake on glucose and insulin metabolism and weight reduction diets in order to make recommendations to limit the risk of diabetes. In fact, many dietary or lifestyle factors such as physical activity, caloric excess, weight gain may be more determinant of the development of metabolic abnormalities that precede the development of diabetes. Moreover, advices have to be made concerning replacement of sugars by other products in case of strict restriction in order to avoid the introduction of other products that could be differently deleterious for health.

Summary conclusion

- All these studies failed to demonstrate an obvious relationship between the intake of total simple carbohydrates and glycaemic control or risk to develop a type 2 diabetes and particularly specific evidence is missing in terms of sucrose effect on diabetes.

- Concerning fructose, there are still discrepancies between studies' conclusions about the long-term deleterious effect on diabetes development. But its effect on lipogenesis and triglyceridemia has to be taken in account, considering the growing use of fructose in food industry and sugar-sweetened drinks.

- More studies are needed in order to determine the impact of strict restriction of simple carbohydrates intake on glucose and insulin metabolism and weight reduction diets in order to make recommendations to limit the risk of

diabetes. Impact of many dietary or lifestyle factors such as physical activity, caloric excess, weight gain have to be taken into account.

- Advices have to be made concerning replacement of sugars by other products in case of strict restriction in order to avoid the introduction of other products that could be differently deleterious for health.

Conflict of Interest Statement

ML has received speaker fees from Benjamin Delessert Institute and from the European Scientific Workshop on Sugars: J-AN declares no conflicts of interest.

References

1. Daly ME, Vale C, Walker M, Alberti KG, Mathers JC. Dietary carbohydrates and insulin sensitivity: a review of the evidence and clinical implications. *Am J Clin Nutr* 1997; **66**: 1072–1085.
2. Sole CC, Noakes TD. Faster gastric emptying for glucose-polymer and fructose solutions than for glucose in humans. *Eur J Appl Physiol Occup Physiol* 1989; **58**: 605–612.
3. Levin RJ. Dietary carbohydrate and the kinetics of intestinal functions in relation to hexose absorption. In: Dobbing J (ed.). *Dietary Starches and Sugars in Man: a Comparison*. Springer-Verlag: London, 1989, pp. 89–117.
4. Ellwood KC, Chatzidakis C, Failla ML. Fructose utilization by the human intestinal epithelial cell line, Caco-2. *Proc Soc Exp Biol Med* 1993; **202**: 440–446.
5. Mahraoui L, Rousset M, Dussaulx E, Darmoul D, Zwiibaum A, Brot-Laroche E. Expression and localization of GLUT-5 in Caco-2 cells, human small intestine, and colon. *Am J Physiol* 1992; **263**: G312–G318.
6. Ravich WJ, Bayless TM, Thomas M. Fructose: incomplete intestinal absorption in humans. *Gastroenterology* 1983; **84**: 26–29.
7. Van den Berghe G. Fructose: metabolism and short-term effects on carbohydrate and purine metabolic pathways. *Prog Biochem Pharmacol* 1986; **21**: 1–32.
8. Delarue J, Normand S, Pachiaudi C, Beylot M, Lamisse F, Riou JP. The contribution of naturally labelled ¹³C fructose to glucose appearance in humans. *Diabetologia* 1993; **36**: 338–345.
9. Tissot S, Normand S, Guilluy R, Pachiaudi C, Beylot M, Laville M, Cohen R, Mornex R, Riou JP. Use of a new gas chromatograph isotope ratio mass spectrometer to trace exogenous ¹³C labelled glucose at a very low level of enrichment in man. *Diabetologia* 1990; **33**: 449–456.
10. Delarue J, Couet C, Lamisse F. Métabolisme du glucose in vivo chez l'homme. *Cah Nutr Diet* 1994; **XXIX**: 205–214.
11. Thiebaud D, Jacot E, Schmitz H, Spengler M, Felber JP. Comparative study of isomalt and sucrose by means of continuous indirect calorimetry. *Metabolism* 1984; **33**: 808–813.
12. Zakim D, Herman RH. The effect of intravenous fructose and glucose on the hepatic alpha-glycerophosphate concentration in the rat. *Biochim Biophys Acta* 1968; **165**: 374–379.
13. Burch HB, Max P Jr, Ghyu, K, Lowry OH. Metabolic intermediates in liver of rats given large amounts of fructose or dihydroxyacetone. *Biochem Biophys Res Commun* 1969; **34**: 619–626.
14. Hoekstra JH, van Kempen AA, Bijl SB, Kneepkens CM. Fructose breath hydrogen tests. *Arch Dis Child* 1993; **68**: 136–138.

15. Pan DA, Lillioja S, Milner MR, Kriketos AD, Baur LA, Bogardus C, Storlien LH. Skeletal muscle membrane lipid composition is related to adiposity and insulin action. *J Clin Invest* 1995; **96**: 2802–2808.
16. Hallfrisch J, Reiser S, Prather ES. Blood lipid distribution of hyperinsulinemic men consuming three levels of fructose. *Am J Clin Nutr* 1983; **37**: 740–748.
17. Reiser S, Handler HB, Gardner LB, Hallfrisch JG, Michaelis OE 4th, Prather ES. Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. *Am J Clin Nutr* 1979; **32**: 2206–2216.
18. Reiser S, Bohn E, Hallfrisch J, Michaelis OE 4th, Keeney M, Prather ES. Serum insulin and glucose in hyperinsulinemic subjects fed three different levels of sucrose. *Am J Clin Nutr* 1981; **34**: 2348–2358.
19. Bantle JP, Laine DC, Thomas JW. Metabolic effects of dietary fructose and sucrose in types I and II diabetic subjects. *JAMA* 1986; **256**: 3241–3246.
20. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary sucrose in type II diabetic subjects. *Diabetes Care* 1993; **16**: 1301–1305.
21. Peterson DB, Lambert J, Gerring S, Darling P, Carter RD, Jelfs R, Mann JL. Sucrose in the diet of diabetic patients – just another carbohydrate? *Diabetologia* 1986; **29**: 216–220.
22. Brynes AE, Frost GS. Increased sucrose intake is not associated with a change in glucose or insulin sensitivity in people with type 2 diabetes. *Int J Food Sci Nutr* 2007; **58**: 644–651.
23. Black RN, Spence M, McMahon RO, Cuskelly GJ, Ennis CN, McCance DR, Young IS, Bell PM, Hunter SJ. Effect of eucaloric high- and low-sucrose diets with identical macronutrient profile on insulin resistance and vascular risk: a randomized controlled trial. *Diabetes* 2006; **55**: 3566–3572.
24. Hallfrisch J, Ellwood KC, Michaelis OE 4th, Reiser S, O'Dorisio TM, Prather ES. Effects of dietary fructose on plasma glucose and hormone responses in normal and hyperinsulinemic men. *J Nutr* 1983; **113**: 1819–1826.
25. Koivisto VA, Yki-Jarvinen H. Fructose and insulin sensitivity in patients with type 2 diabetes. *J Intern Med* 1993; **233**: 145–153.
26. Crapo PA, Kolterman OG, Henry RR. Metabolic consequence of two-week fructose feeding in diabetic subjects. *Diabetes Care* 1986; **9**: 111–119.
27. Thorburn AW, Crapo PA, Griver K, Wallace P, Henry RR. Long-term effects of dietary fructose on carbohydrate metabolism in non-insulin-dependent diabetes mellitus. *Metabolism* 1990; **39**: 58–63.
28. Le KA, Faeh D, Stettler R, Ith M, Kreis R, Vermathen P, Boesch C, Ravussin E, Tappy L. A 4-wk high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. *Am J Clin Nutr* 2006; **84**: 1374–1379.
29. Saris WHM, Astrup A, Prentice AM, Zunft HJF, Formiguera X, Verboeket-van de Venne WPHG, Raben A, Poppitt SD, Seppelt B, Johnston S, Vasilaras TH, Keogh GF. Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs. complex carbohydrates on body weight and blood lipids: the CARMEN study. *Int J Obes* 2000; **24**: 1310–1318.
30. Meyer KA, Kushi LH, Jacobs DR Jr, Slavin, J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 2000; **71**: 921–930.
31. Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 1997; **20**: 545–550.
32. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA* 1997; **277**: 472–477.
33. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001; **345**: 790–797.
34. Montonen J, Jarvinen R, Knekt P, Heliövaara M, Reunanen A. Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. *J Nutr* 2007; **137**: 1447–1454.
35. Janket SJ, Manson JE, Sesso H, Buring JE, Liu S. A prospective study of sugar intake and risk of type 2 diabetes in women. *Diabetes Care* 2003; **26**: 1008–1015.
36. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA* 2004; **292**: 927–934.
37. Buyken AE, Toeller M, Heitkamp G, Karamanos B, Rottiers R, Muggeo M, Fuller JH. Glycemic index in the diet of European outpatients with type 1 diabetes: relations to glycosylated hemoglobin and serum lipids. *Am J Clin Nutr* 2001; **73**: 574–581.
38. Wolever TM, Hamad S, Chiasson JL, Josse RG, Leiter LA, Rodger NW, Ross SA, Ryan EA. Day-to-day consistency in amount and source of carbohydrate intake associated with improved blood glucose control in type 1 diabetes. *J Am Coll Nutr* 1999; **18**: 242–247.
39. Sevak L, McKeigue PM, Marmot MG. Relationship of hyperinsulinemia to dietary intake in south Asian and European men. *Am J Clin Nutr* 1994; **59**: 1069–1074.

Added sugars and micronutrient dilution

M. B. E. Livingstone¹ and K. L. Rennie²

¹Northern Ireland Centre for Food and Health, School of Biomedical Sciences, University of Ulster, Coleraine, Co. Londonderry, UK;

²University of Hertfordshire, Hatfield, Hertfordshire, UK.

Received 30 October 2008; accepted 19 November 2008

Address for correspondence: MBE Livingstone, Northern Ireland Centre for Food and Health, School of Biomedical Sciences, University of Ulster, Coleraine, Co. Londonderry BT52 1SA, UK. E-mail: mbe.livingstone@ulster.ac.uk

Summary

There is increasing concern that high intakes of added sugars promote micronutrient dilution. However, the overall conclusion to emerge from the existing evidence base is that associations between reported intakes of added sugars and intakes of micronutrients are inconsistent and often non-linear, both across and within age groups, and between the genders. If a nutrient displacement effect does exist, a high consumption of added sugar does not necessarily compromise overall micronutrient intakes and similarly, consuming less added sugar is no guarantee that micronutrient intakes will be optimized. Clarification of this issue has been beset by methodological and conceptual difficulties. The observed associations between added sugars and micronutrient intake have been heavily contingent on both the definition of sugars chosen and the analytical approach used for adjusting for differences in reported energy intake. These issues have been further compounded by mis-reporting of food intake of unknown direction and magnitude and the cut-offs used to determine 'inadequate' micronutrient intakes which vary over time and between studies and countries. In the absence compelling evidence that micronutrient intakes are compromised by a high consumption of added sugars, it may now be appropriate to question the legitimacy of the nutrient dilution hypothesis as it is highly likely that it is oversimplifying more subtle and complex dietary issues. Recommendations for further research are made to help bring resolution to these issues.

Keywords: Micronutrient dilution, review, sugars.

obesity reviews (2009) **10** (Suppl. 1), 34–40

Introduction

Concerns about sugars and health are long standing and undoubtedly one of the most persistent concerns of many nutritionists is that a high consumption of added sugars can, through displacement of more nutrient dense foods from the diet, dilute the nutrient density of the diet. This dilution hypothesis and the concept of 'empty calories' has been the subject of much debate, even controversy in both the scientific and popular literature with, as yet, no consensus on the issue. The aim of this review is to evaluate methodological constraints and conceptual issues which impede resolution of this controversy.

The evidence base

An extensive primary database on the subject of sugars and micronutrient dilution now exists. By far the majority of

studies have been cross-sectional observational studies of varying size and representativeness. In contrast, there has been a paucity of intervention studies on the issue (1–4). In the majority of cross-sectional studies, food intakes have been self-reported by a range of methods each of which have their own inherent limitations but where the common primary concern relates to pervasive under-reporting of food intake (5). Only two studies have examined biochemical indices of micronutrient status, both in elderly populations (6,7), while the majority of studies have used group recommended intakes and varying cut-off criteria to determine 'adequacy' of intakes. Sugars have been defined in various ways, most usually as total sugars, added sugars or non-milk extrinsic sugars (NMES), which makes it difficult to make nutritionally meaningful comparisons between studies.

Since 1995, seven reviews on the topic have been published and while these have varied in both scope and

emphasis they have all come to broadly similar conclusions (8–14). Overall, these reviews provide no clear or compelling evidence for micronutrient dilution in the face of high intakes of added sugars. Although a recurring theme in all of the reviews is one of inconsistency between study outcomes, there is general consensus that total energy intake is positively associated with total nutrient intakes and the likelihood of achieving recommended intakes. Therefore, in the context of an appropriate energy intake, it appears that a wide range of sugar intake can be tolerated without detriment to micronutrient intakes. The risk of low micronutrient intakes appears to be greatest in diets that are characterized by high % energy from sugars at low levels of energy intake.

Even where studies do show evidence of a dilution effect, the nutritional significance of high added sugar consumption is strongly nutrient specific and often non-linear with the highest nutrient intakes being observed among average sugar consumers relative to low and high categories of intake (6,15). It is not clear why this is the case, but non-linear trends in reported energy intake (lower energy intakes in the lowest and highest sugar intake categories) as a result of differential mis-reporting is highly conceivable. Moreover, in most cases where specific micronutrients are inversely correlated with sugar consumption, this does not appear to be problematic in the total dietary context as intakes are still above those recommended. Overall, it has concluded that while nutrient intakes show a downward trend with increasing sugar (expressed as NMES) intakes, this is of little nutritional consequence at intakes up to 20% energy from NMES (14).

Available data on children derived from a range of age groups show varying associations between intakes of added sugars and micronutrients. Added sugar (expressed as % energy) intake tends to increase with age among young people (16,17), while the reverse has been observed with micronutrient intakes, particularly for micronutrients such as folate, vitamin C and calcium (18). However, with the exception of calcium, where some studies have reported intakes below those recommended in the higher added sugars consumers (16,19–21), intakes of micronutrients appear to be compatible with a broad range of sugar intakes. A number of the more recent reviews (12–14) have raised concerns about the negative impact of both escalating intakes of sugar sweetened soft drinks and declining milk consumption on micronutrient intakes.

In summary, despite the extensive literature on the topic, the totality of the data to date does not provide convincing evidence to either support or refute the micronutrient dilution hypothesis. Clarification of this issue has been beset by a range of methodological and conceptual constraints, which are discussed later.

Sugar terminology

The definitions and classifications used to evaluate patterns of sugar consumption are particularly pertinent in the context of clarifying their role in micronutrient displacement. At present, however, because of the plethora of different definitions of dietary sugars and a lack of consensus about how best to categorize them, meaningful comparisons between studies are very difficult (22). Conventionally, the term 'sugars' is used to describe the mono- and disaccharides, whether added or naturally present in foods. However, in the USA the term 'added sugars' is used to define those sugars, sweeteners and syrups that are eaten as such or used as ingredients in processed and prepared foods, excluding sugars present in milk and fruit (23). Meanwhile, in Europe there is no consistent approach to classifying sugars. In the UK the categorization of NMES is favoured, being defined as all extrinsic sugars (all sugars not contained within the cellular structure of foods) except those present in milk and milk products. NMES are similar but not identical to added sugars as the former categorization incorporates sugars that are found in fruit juices and 50% of the sugars in cooked and processed fruit (22). No other European country uses this classification system; they instead use terminologies such as added or total sugars, the latter including fruit and milk sugars. Not surprisingly, owing to the inclusion of the latter foods, studies evaluating the impact of total sugars generally show a positive relationship with calcium and vitamin C densities (24), whereas studies that have focussed on NMES are more likely to detect a negative association with calcium intakes but a positive association with vitamin C intakes (25). Gibson (15) has also demonstrated that different conclusions can be drawn from the same data set depending on whether NMES or added sugars are used in the analysis. For example, in adult men vitamin C intakes were significantly positively associated with NMES intakes, while being significantly inversely associated with added sugar intakes. Clearly, the many different ways of classifying sugars has hindered the interpretation of the literature, and will continue to do so until clarity and consensus is reached about the most appropriate terminology to use.

Approaches used to adjust energy intake

Another major and also unresolved issue in this debate is the most appropriate analytical approach to use for adjusting energy intakes. The two main approaches include categorization of sugar consumption by absolute intakes (g d^{-1}) and % energy provided by sugar. When expressed in absolute terms the available data show that, in most cases, absolute nutrient intakes are positively associated with intakes of added sugars (24,26–28). Thus diet quality may not necessarily be compromised at higher added sugar

intakes simply because energy intakes appear to be more predictive of micronutrient intakes. The relatively weak independent effect of added sugars on micronutrient intakes has been demonstrated by Charlton *et al.* (7) who showed that more of the variation in the daily micronutrient intakes of elderly subjects was accounted for by differences in energy intake than by added sugar intake. Similarly, it has been noted that total food energy of British elderly subjects was a more significant predictor of their micronutrient intakes than were NMES (6). Thus, the risk of low micronutrient intake is likely to be greatest in those groups whose diets are characterized by a low total energy intake and high % energy from added sugars (6,29), and could well become an increasing problem across all age groups as energy requirements decline because of more inactive lifestyles.

In order to evaluate the independent association of sugar on micronutrient intakes virtually all studies have expressed added sugar as per cent of energy intake. However, such an adjustment may not be sufficient as % energy from added sugars is influenced by the absolute intakes of the other macronutrients. As a result it cannot segregate the association between added sugars and micronutrient intake from that of either total energy or energy from other macronutrients, particularly fat (30).

Expressing sugar intake as a ratio variable with total energy intake makes it difficult to interpret results because the ratio is composed of two variables and thus any change in the ratio could be due to a change in either sugar or energy intake. An additional complication is that added sugar energy, being a component of total energy intake, creates a dependency between the numerator (added sugar intake) and the denominator (total energy intake), thus rendering it impossible to determine which one is the true predictor of micronutrient intake (30). Two alternative approaches to analysing the NHANES III data set – one based on % added sugar energy (23) and the other on multiple regression analysis to partition total energy from added sugars from other energy sources (30) – illustrate how opposing conclusions may be drawn from the same data based on the analytical approach used. In contrast to the former analysis which reported an inverse association between intakes of calcium, vitamin A, iron and zinc and % added sugar energy, the latter analysis concluded that energy from sources other than added sugars had a much stronger, positive and consistent association with micronutrient intakes than energy from added sugars, which had little substantive effect on diet quality.

It is important to note that there is no optimal approach to adjusting for variations in reported energy intake and the analytical approach favoured by Forshee and Storey (30) has also been criticized for not controlling appropriately for total energy intake (31). Adjusting for energy intake allows comparisons across age groups and takes into

account the higher energy needs of larger individuals but, at the same time, any method of adjustment does have its limitations. The nutrient density method (micronutrient intake/energy intake) does not totally remove the effect of energy intake in the model. The nutrient residual method, derived by regressing energy intake on added sugars and then entering the residuals from this regression model, is susceptible to misspecification as other important variables, such as age and gender, are significantly related to the omitted energy intake variable. Adding energy intake as a separate covariate appears to be the best method to adjust for energy intake levels, but it could also be argued that the problem of multicollinearity still remains as energy intake is so highly correlated as a covariate with sugar intake (30).

Although the various approaches for energy adjustment have their strengths and limitations, it needs to be emphasized that any conclusions about micronutrient dilution by sugars will be contingent on the methodology favoured and merit much more debate in order to determine the best statistical method(s) to apply when evaluating nutrient displacement issues.

Criteria of adequacy

As micronutrient requirements are largely unknown and true risk of inadequacy can only be assessed by biochemical indices, adequacy of micronutrient intake is most usually judged against group recommended intakes. In most studies a broad range of sugar intakes appear to be compatible with adequate micronutrient intake although the criteria for what constitutes ‘adequacy’ varies between studies. These inconsistencies arise as a result of differences between countries in their dietary recommendations, changes in recommendations over time and the cut-offs used. Although the estimated average requirement is now recognized as the most appropriate cut-off (32) to use in evaluating nutrient intakes, many researchers have chosen instead to examine the number of subjects achieving the reference nutrient intake (RNI) or intakes as a percentage (usually two-thirds) of the RNI. Such cut-offs, particularly the former, are likely to overestimate the true prevalence of inadequate intakes. In contrast, in those studies that have used the lower reference nutrient intakes as the yardstick, prevalence will be underestimated. Consequently, no firm conclusions are justified about the nutritional significance of the dilutional effects of added sugars based on the existing data.

Mis-reporting of food intake

Bias in self-reported dietary intake, particularly due to under-reporting, is now a well-documented phenomenon in dietary surveys (5) and is highly likely to mask associations between added sugar and micronutrient intakes. However,

in many studies in this area there is little information about the potential level of under-reporting and no adjustment for, or exclusion of, under-reporters. Under-reporting of food intake tends to be a selective rather than a general phenomenon. In adults some studies have identified selective under-reporting of sweetened foods and beverages particularly by overweight individuals (33,34). Other studies have also observed that under-reporting appears to be more prevalent in those subjects categorized as having low intakes of added sugars (15,25).

Thus it is highly probable that in the existing data sets added sugars intakes have been selectively under-reported. It is also far from certain which micronutrients might be most affected by this reporting bias, but this will produce serious overestimates of inadequate intakes. Where possible, it is important to adopt more than one analytical approach in order to fully evaluate the impact of under-reporting, particularly selective under-reporting on micronutrient dilution.

Added sugars in the dietary context

All of the evidence to date suggests that high-added sugar consumption does not automatically result in a diet of inadequate micronutrient intake. Diets are inherently complex and it is perhaps conceptually naïve to suggest that a nutrient bereft food such as sugar will automatically displace micronutrient-dense foods from the diet to the point where micronutrient intake is compromised. This issue can only be properly addressed by a close scrutiny of both the forms and the ways that sugars are consumed within the context of the total diet in order to draw nutritionally meaningful conclusions from the data (12). For example, it is normal dietary practice for a number of foods to be consumed together and this may lead to micronutrient intake profiles that would not be observed if the added sugar component was examined separately. Thus, if a primary source of added sugar is sweetened ready-to-eat cereal products, higher intakes of vitamin D and calcium may be observed because of the usual dietary behaviour of consuming cereal with milk (35,36).

Overall, sweetened dairy foods, milk drinks and cereals are more likely to positively impact on diet quality, in contrast to soft drinks, sugars, sweets and sweetened grain products such as biscuits and cakes, which are more likely to have an adverse impact, particularly on intakes of calcium, iron and folate (36). When the latter group examined associations between the five major dietary sources of sugar in US children and adolescents with calcium, folate and iron intakes distinctly different intake patterns were observed depending on the source of the added sugars. For example, iron intakes were consistently lower in the highest consumers of sugar-sweetened beverages, sweets

and sweetened grains but were higher with higher intakes of pre-sweetened cereals.

The fortification of foods such as breakfast cereals with key nutrients, particularly vitamins B1, B2, B3, B6, folate, vitamin C and iron, undoubtedly help to counteract nutrient displacement attributable to added sugars. Studies in children and adolescents (35,37), in adults (38) and in the elderly (39) have shown that the highest consumers of fortified ready-to-eat breakfast cereals can obtain substantial amounts of their daily intakes of some vitamins such as B1, B2 and folate from these foods. In the analysis of the DONALD database of nearly 5000 three-day weighed dietary records in children and adolescents it was concluded that sweetened fortified foods such as breakfast cereals tended to counteract dilution of most micronutrients owing to added sugars (40). Therefore, although higher added sugar consumption may lead to lower nutrient density, the magnitude of this effect may be reversed, or at least partially offset, by food fortification of some commonly consumed sugar-sweetened foods.

Probably one of the most controversial, often emotive, issues is the nutritional impact of the escalating consumption levels of sugar sweetened soft drinks, particularly in children where they contribute more than half of the added sugars derived from the diet (16,19,20,41). Overall, significantly lower intakes of some micronutrients such as vitamin A, riboflavin, folate, calcium and magnesium have been observed among high consumers of sugar-sweetened beverages (36,42–45). On the other hand, consumption of sugar-sweetened beverages, which are fortified with either vitamin C or vitamin C-containing fruit juices, may account for the positive association of vitamin C with added sugars (44) or total NMES (25).

Concurrent with the increase in sugar-sweetened beverages there has been a secular trend towards decreasing milk consumption in children over the past 20 years (46). This has led some researchers to propose a displacement effect in children's diets (36,44,45,47,48), particularly in relation to calcium intakes (49). However, it is still unclear whether this is a cause-and-effect relationship. It is also not inevitable that sweetened soft drink consumption is associated with poor calcium status as this may be partially offset by increased consumption of other dairy products such as sugar-sweetened milk drinks. (46,50,51).

In the context of sugar-fat associations, many studies that have evaluated the 'empty calorie' hypothesis have observed an inverse association between relative (% energy) added sugar intake and fat intake, an association that appears to be consistent across all age groups (20,25–27,52). Thus, it is entirely conceivable that dietary fat intake, if not adjusted for, may bias the estimated effect of added sugars on diet quality. For example, added sugars are often negatively associated with intakes of fat-soluble vitamins, but it has been demonstrated that when fat intake was statistically

controlled for, the intakes of the latter had a much larger negative association with Vitamin A than did added sugars (18). Although there is still no consensus on the most valid approach to energy adjustment, the analyses by Forshee and Storey (18) clearly demonstrate that if specification errors are to be avoided, the impact of added sugars on diet quality must be evaluated in the total dietary context. Depending on the dietary choices made, other macronutrients may be more important predictors of micronutrient intakes than added sugars (18). Finally, it is worthwhile remembering that because of the inverse association between fat and sugar intakes, any advice to limit consumption of foods high in added sugar may have the counterproductive effect of increasing the intake of dietary fat.

Conclusions

The overall conclusion to emerge from the existing studies and reviews in the area is that associations between reported intakes of added sugars (whether expressed in absolute [g d^{-1}] or relative [% energy] terms) and intakes of micronutrients are inconsistent and often non-linear, both across and within age groups, and between the genders. Clarification of this issue has been beset by methodological and conceptual difficulties. The observed associations between added sugars and micronutrient intake have been heavily contingent on both the definition of sugars chosen and the analytical approach used for adjusting for differences in reported energy intake. These issues have been further compounded by mis-reporting of food intake of unknown direction and magnitude and the cut-offs used to determine 'inadequate' micronutrient intakes that vary over time and between studies and countries.

If a nutrient displacement effect does exist, it appears that a high consumption of added sugar does not necessarily compromise overall micronutrient intakes, unless diets are also low in energy. Similarly, consuming less added sugar is no guarantee that micronutrient intakes will be optimized. In the absence of consistent and compelling evidence linking added sugars with micronutrient depletion, there seems to be little merit in, and no justification for, setting quantitative recommendations for upper levels of added sugars intake because of concerns about micronutrient dilution. Rather than vilifying foods such as added sugars, the promotion of foods with a high ratio of nutrients to energy against a background of variety, balance and moderation may be a better strategy for improving overall diet quality.

Indeed, given the inherent complexity of diets it may now be appropriate to question the legitimacy of the whole nutrient dilution hypothesis as it is highly likely that it is oversimplifying more subtle and complex dietary issues. The following recommendations for further research are

made to help bring more clarity to this long-standing, often emotive debate.

- The food supply with respect to carbohydrates is becoming more complex, making it increasingly difficult to distinguish between natural and added sugars. Given that sugars are indistinguishable chemically and physiologically it may not be feasible, or even necessary, to make the distinction. At present, however, associations between sugars and micronutrient intakes are contingent on the definition used and, even within the same dataset, can give rise to inconsistent relationships. These issues need resolution by reaching consensus on how to categorize both total and added sugars in a less arbitrary way and by reporting their respective intakes in dietary surveys. Only then will it be possible to justify (or not) that such a distinction is nutritionally meaningful.

- Currently, there is no optimal approach, let alone agreement, on how to adjust for variations in total energy intake. As a result, different adjustment techniques applied to the same data sets have generated divergent conclusions about micronutrient displacement. Similarly, the common analytical practice of isolating added sugars from the total diet may generate specification error and bias the estimated effect of added sugars on micronutrient dilution. These issues merit much greater debate and scrutiny in order to understand the main drivers of micronutrient intake and diet quality.

- Although intervention studies in this area would be very difficult logistically, they remain the only way to definitively answer if the inverse association between the intakes of milk and sugar-sweetened soft drinks in children is one of cause or effect. Such studies would also need to address not only the impact on diet quality of the interventions but also their likely acceptability and sustainability. Prospective intervention studies are also needed to assess the impact of alterations in added sugars (and other macronutrients) on micronutrient intakes.

- The term 'empty calories' is an oversimplification of a complex issue, and before issuing public health advice about moderating sugar intakes the diet as a whole should be considered. It has been shown (27) that high added sugar consumers are likely to have a different pattern of intake for a wide range of foods and as a consequence simply focussing on a reduction of added sugars alone will not necessarily improve overall quality of the diet unless other aspects of the diet are also addressed.

- Although progress has been made in better identifying mis-reporting in dietary surveys, the role of under-reporting in masking associations between sugar intakes and micronutrient intakes remains far from clear and needs more thorough investigation. Consensus on how to adjust dietary data to allow for both random and systematic error is also required.

• Perhaps the issue of micronutrient dilution can only be resolved by initiating new research designed specifically to address the issue, with specific hypotheses, sufficient statistical power and using dietary methodologies and statistical techniques that are fit for purpose. Rather than focusing primarily on added sugars as being uniquely detrimental to overall micronutrient intakes, their impact needs to be judged within the total dietary context. Where micronutrient dilution can be attributed to added sugar, analyses should quantify the magnitude, as well as the direction, of any observed significant associations between intakes of added sugars and micronutrients.

Conflict of Interest Statement

Professor Livingstone has received a grant from Unilever; Dr Rennie has received a grant from the British Sugar Bureau.

References

1. Heaton KW, Emmett PM, Henry CL, Thornton JR, Manhire A, Hartog M. Not just fibre – the nutritional consequences of refined carbohydrate foods. *Hum Nutr Clin Nutr* 1983; 37: 31–35.
2. Cline AD, Tharion WJ, Tulley RT, Hotson N, Lieberman HR. Influence of a carbohydrate drink on nutritional status, body composition and mood during desert training. *Aviat Space Environ Med* 2000; 71: 37–44.
3. West JA, de Looy AE. Weight loss in overweight subjects following low-sucrose or sucrose-containing diets. *Int J Obes Relat Metab Disord* 2001; 25: 1122–1128.
4. Vasilaras TH, Astrup A, Raben A. Micronutrient intake in overweight subjects is not deficient on an ad libitum fat-reduced, high simple carbohydrate diet. *Eur J Clin Nutr* 2004; 58: 326–336.
5. Livingstone MBE, Black AE. Markers of the validity of reported energy intake. *J Nutr* 2003; 133: S895–S920.
6. Gibson S. Dietary sugars and micronutrient dilution in normal adults aged 65 years and over. *Public Health Nutr* 2001; 4: 1235–1244.
7. Charlton KE, Kolbe-Alexander TL, Nel JH. Micronutrient dilution associated with added sugar intake in elderly black South African women. *Eur J Clin Nutr* 2005; 59: 1030–1042.
8. Gibney M, Sigman-Grant M, Stanton JL, Keast DR. Consumption of sugars. *Am J Clin Nutr* 1995; 65: S178–S194.
9. Bolton-Smith C. Intake of sugars in relation to fatness and micronutrient adequacy. *Int J Obes Relat Metab Disord* 1996; 20(Suppl. 2): S31–S33.
10. Ruxton CH, Garceau FJ, Cottrell RC. Guidelines for sugar consumption in Europe: is a quantitative approach justified? *Eur J Clin Nutr* 1999; 53: 503–513.
11. Ruxton CH. Dietary guidelines for sugar: the need for evidence. *Br J Nutr* 2003; 90: 245–247.
12. Murphy SP, Johnson RK. The scientific basis of recent US guidance on sugars intake. *Am J Clin Nutr* 2003; 78: S827–S833.
13. Rennie KL, Livingstone MBE. Associations between dietary added sugar intake and micronutrient intake: a systematic review. *Br J Nutr* 2007; 97: 832–841.
14. Gibson SA. Dietary sugars and micronutrient adequacy: a systematic review of the evidence. *Nutr Res Rev* 2007; 20: 121–131.
15. Gibson SA. Do diets high in sugars compromise micronutrient intakes? *J Hum Nutr Diet* 1997; 10: 125–133.
16. Øverby NC, Lillegaard IT, Johansson L, Andersen LF. High intake of added sugar among Norwegian children and adolescents. *Public Health Nutr* 2004; 7: 285–293.
17. Joyce T, McCarthy SN, Gibney MJ. Relationship between energy from added sugars and frequency of added sugars intake in Irish children, teenagers and adults. *Br J Nutr* 2008; 99: 1117–1126.
18. Forshee RA, Storey ML. The role of added sugars in the diet quality of children and adolescents. *J Am Coll Nutr* 2001; 20: 32–43.
19. Lyhne N, Ovesen L. Added sugar and nutrient density in the diet of Danish children. *Scand J Nutr* 1999; 43: 4–7.
20. Alexy U, Sichert-Hellert W, Kersting M. Associations between intake of added sugars and intakes of nutrients and food groups in the diets of German children and adolescents. *Br J Nutr* 2003; 90: 441–447.
21. Kranz S, Smiciklas-Wright H, Siega-Riz AM, Mitchell D. Adverse effect of high added sugar consumption on dietary intake in American preschoolers. *J Pediatr* 2005; 146: 105–111.
22. Kelly SA, Summerbell C, Rugg-Gun AJ, Adamson A, Flectcher E, Moynihan PJ. Comparison of methods to estimate non-milk extrinsic sugars and their application to sugars in the diet of young adolescents. *Br J Nutr* 2005; 94: 114–124.
23. Institute of Medicine of the National Academies. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. National Academies Press: Washington DC, 2002.
24. Gibson SA. Consumption and sources of sugars in the diets of British schoolchildren: are high-sugar diets nutritionally inferior? *J Hum Nutr Diet* 1993; 6: 355–371.
25. Gibson SA. Non-milk extrinsic sugars in the diets of preschool children: association with intakes of micronutrients, energy, fat and NSP. *Br J Nutr* 1997; 78: 367–378.
26. Rugg-Gunn A, Hackett A, Jenkins G, Appleton D. Empty calories? Nutrient intake in relation to sugar intake in English adolescents. *J Hum Nutr Diet* 1991; 4: 101–111.
27. Baghurst K, Baghurst P, Record S. Demographic and nutritional profiles of people consuming varying levels of added sugars. *Nutr Res* 1992; 12: 1455–1465.
28. Lewis C, Park Y, Dexter P, Yetley E. Nutrient intakes and body weights of persons consuming high and moderate levels of added sugars. *J Am Diet Assoc* 1992; 92: 708–713.
29. Charlton KE, Wolmarans P, Lombard CJ. Evidence of nutrient dilution with high sugar intakes in older South Africans. *J Hum Nutr Diet* 1998; 11: 331–343.
30. Forshee RA, Storey ML. Controversy and statistical issues in the use of nutrient densities in assessing diet quality. *J Nutr* 2004; 134: 2733–2737.
31. Barr SI, Johnson RK. Effect of added sugars on dietary quality. *J Nutr (Lett)* 2005; 135: 1336.
32. Institute of Medicine Food and Nutrition Board. *Dietary Reference Intakes: Applications in Dietary Planning*. National Academies Press: Washington DC, 2003.
33. Poppitt SD, Swann D, Black AE, Prentice AM. Assessment of selective under-reporting of food intake by both obese and non-obese women in a metabolic facility. *Int J Obes Relat Metab Disord* 1998; 22: 303–311.
34. Krebs-Smith SM, Graubard BI, Kahle LL, Subar AF, Cleveland LE, Ballard-Barbash R. Low energy reporters vs others: a comparison of reported food intakes. *Eur J Clin Nutr* 2000; 54: 281–287.
35. Morgan K, Zabik M, Leveille G. The role of breakfast in nutrient intake of 5- to 12-year-old children. *Am J Clin Nutr* 1981; 34: 1418–1427.

36. Frary CD, Johnson RK, Wang MQ. Children and adolescents' choices of foods and beverages high in added sugars are associated with intakes of key nutrients and food groups. *J Adolesc Health* 2004; **34**: 56–63.
37. Albertson AM, Anderson GH, Crockett SJ, Goebel MT. Ready-to-eat cereal consumption: its relationship with BMI and nutrient intake of children aged 4 to 12 years. *J Am Diet Assoc* 2003; **103**: 1613–1619.
38. Galvin MA, Kiely M, Flynn A. Impact of ready-to-eat breakfast cereal (RTEBC) consumption on adequacy of micronutrient intakes and compliance with dietary recommendations in Irish adults. *Public Health Nutr* 2003; **6**: 351–363.
39. Morgan K, Zabik M. The influence of ready-to-eat cereal consumption at breakfast on nutrient intakes of individuals 62 years and older. *J Am Coll Nutr* 1984; **3**: 27–44.
40. Alexy U, Sichert-Hellert W, Kersting M. Fortification masks nutrient dilution due to added sugars in the diet of children and adolescents. *J Nutr* 2002; **132**: 2785–2791.
41. Guthrie JF, Morton JF. Food sources of added sweeteners in the diets of Americans. *J Am Diet Assoc* 2000; **100**: 43–51.
42. Guenther PM. Beverages in the diets of American teenagers. *J Am Diet Assoc* 1986; **86**: 493–499.
43. Harnack L, Stang J, Story M. Soft drink consumption among US children and adolescents: nutritional consequences. *J Am Diet Assoc* 1999; **99**: 436–441.
44. Ballew C, Kuester S, Gillespie C. Beverage choices affect adequacy of children's nutrient intakes. *Arch Pediatr Adolesc Med* 2000; **154**: 1148–1152.
45. Mrdjenovic G, Levitsky DA. Nutritional and energetic consequences of sweetened drink consumption in 6- to 13-year-old children. *J Pediatr* 2003; **142**: 604–610.
46. Niklas T, Myers L, Beech B, Berenson GS. Trends in dietary intake of sugars of 10-year old children from 1973 to 1988: the Bogulusa Heart Study. *Nutr Res* 1999; **19**: 519–530.
47. Harnack L, Stang J, Story M. Soft drink consumption among US children and adolescents: nutritional consequences. *J Am Diet Assoc* 1999; **99**: 436–441.
48. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med* 2004; **27**: 205–210.
49. Krebs-Smith SM. Choose beverages and foods to moderate your intake of sugars: measurement requires quantification. *J Nutr* 2001; **131**: S527–S535.
50. Johnson RK, Frary C, Wang MQ. The nutritional consequences of flavoured milk consumption by school-aged children and adolescents in the United States. *J Am Diet Assoc* 2002; **102**: 853–856.
51. Rodríguez-Artalejo F, García EL, Gorgojo L, Garcés C, Royo MA, Martín Moreno JM, Benavente M, Macías A, De Oya M. Investigators of the Four Provinces Study. Consumption of bakery products, sweetened soft drinks and yoghurt among children aged 6–7 years: association with nutrient intake and overall diet quality. *Br J Nutr* 2003; **89**: 419–429.
52. Kranz S, Smiciklas-Wright H, Siega-Riz AM, Mitchell D. Adverse effect of high added sugar consumption on dietary intake in American preschoolers. *J Pediatr* 2005; **146**: 105–111.

Sucrose and dental caries: a review of the evidence

C. A. Anderson, M. E. J. Curzon, C. Van Loveren, C. Tatsi and M. S. Duggal

Department of Paediatric Dentistry, Child
Dental Health, Leeds Dental Institute, Leeds,
UK

Received 30 October 2008; revised 24
November 2008; accepted 25 November
2008

Address for correspondence: Professor MS
Duggal, Child Dental health, Leeds Dental
Institute, Clarendon Way, Leeds LS2 9LU, UK.
E-mail: m.s.duggal@leeds.ac.uk

Summary

The aim of this study was to conduct a review of the literature to assess the relationship between quantity and pattern of sucrose use and dental caries. Using hand and electronic methods (MEDLINE, EMBASE) the literature was searched for epidemiological papers concerning any relationship of sugars and dental caries published since 1856. Superficial hand searching was carried out between 1856 and 1940, detailed hand searching 1940–1966 and electronic 1966–2007. Selection criteria were set based on, but not confined to, Cochran style standards. Investigations were categorized as A, fulfilling all criteria; B1, relevant fulfilling 19 of 23 criteria; B2, relevant but fulfilling only between 12 and 18 of the selection criteria; and C, all other papers. There were 95 papers meeting most (more than 12) or all of the selected criteria. Only 1 paper was graded A; 31 as B1. There were in addition some 65 as B2 and all the rest as C, which were discarded. There were a wide variety of study designs and those graded A or B1 comprised 23 ecological cross-sectional, 7 cohort and 2 case control studies. Summary results showed that 6 papers found a positive, significant relationship of sugar quantity to dental caries, 19 of 31 studies reported a significant relationship of sugar frequency of use to dental caries. The balance of studies does not demonstrate a relationship between sugar quantity, but a moderately significant relationship of sugar frequency to dental caries.

Keywords: Dental caries, sugar.

obesity reviews (2009) **10** (Suppl. 1), 41–54

Introduction

The sweet taste is inherent in humans, and for centuries the main sweetener available was honey; sugar from sugar cane (khandi) came from India and was extremely expensive. A reappraisal of the evidence from Stone Age, Antiquity, the Middle Ages and early modern times suggests ordinary people ate large quantities of honey (1). Indeed, intakes at various historical times may well have rivalled current consumptions of refined sugar. The change from honey to refined sugar only occurred during the industrial revolution when the manufacture and distribution of refined white sugar coincided with the rapid increase in dental caries.

There are very early references to sugar or sweet foods and dental caries by Fauchard (2) and shortly afterwards by Berdmore (3) who wrote that 'where sugar, tea coffee and sweetmeats are used in excess, the people even at an early age are remarkable for the badness of their teeth'. Miller (4)

first showed experimentally the relationship of refined carbohydrates to caries, as the acidogenic theory, but in fact concentrated his work on potatoes. Since then, some authors have placed great importance on the role of sucrose in the diet. For example, it has been recommended that free sugar consumption should be below 15 kg per person per year in industrialized countries (5). These conclusions were based on World Health Organization (WHO) and Committee on Medical Aspects of Food policy, known as COMA (UK) reports. Sugars were defined by the COMA report and described as either *intrinsic* or *extrinsic* dependent on their basis for metabolism (6). These terms (intrinsic and extrinsic) have been adopted and used within the dental profession in the UK; however, the usefulness of such terms has been questioned (7).

Sucrose has been described as the 'Arch Criminal' of dental caries (8), and he related this to its specific properties pointing out that sucrose, a disaccharide, as being the most

important sugar in the production of extracellular polysaccharides. Sucrose can be broken down directly by extracellular bacterial invertases to form glucose and fructose molecules to produce extracellular polysaccharides having a dual function namely to form a structural matrix of dental plaque and a reservoir of substrate for plaque microorganisms (8). The functional structure of the matrix enables the plaque bacteria to adhere to the enamel surface. Because of these properties sucrose has been described as the main cause of dental caries based on anecdotal and research reports. Such dietary studies, documented and recorded in the dental literature, have been carried out on humans, animals and in the laboratory for over 100 years. There are three main types of human study and they include cross-sectional studies, longitudinal studies and intervention studies.

Cross-sectional studies form the basis of most epidemiological surveys and relate social and environmental factors to disease prevalence. Reports have used this type of observational approach and conclusions are made as to possible cause and effects. Early work (9), for example, related dental caries in the East Greenland Eskimo (Inuit) dentitions to a change in lifestyle from a diet dominated by meat and fat to one of starches and sugars. Later, a study widely known as the Hopewood House Study (10) reported on the percentage of caries free mouths for children that was assumed to be related to the use of a lacto-vegetarian diet, compared with free living children who had a higher use of sucrose. *Longitudinal studies* are represented by the Tristan da Cunha report (11), where an increase in caries was related to evacuation to England between 1961 and 1963 following a volcanic eruption on the island. An increase in dietary consumption of sugars was paralleled by a rapid rise in caries experience. *Intervention studies*, such as the Vipeholm study (12), carried out in an institution for the mentally retarded in Sweden, where the effects of various changes in carbohydrate intake were related to dental caries incidence.

Sugar caries relationships and possible recommendations

These have been studied extensively in a number of different ways. A through review of the literature of diet and dental caries, involving many investigations relating frequent intake of sugar products and dental caries (13) suggested that the aim of prevention of dental diseases was to decrease both the amount of sugar consumed and frequency of intake. Some authors (5) supported the 'safe limit' theory and postulated that a sugar caries sigmoid curve existed. At levels of less than 10 kg per person per year the incidence of caries was reported to be low. At a value of more than 15 kg the incidence increased more rapidly. A maximum of sugar use of 15 kg per person per

year in industrialized countries was therefore proposed (5). Although the dental evidence to support this figure was presented in the paper, this value has never been tested. On the other hand, Cleaton-Jones *et al.* (14) did not support the evidence that a direct relationship existed between sugar consumption and dental caries prevalence and contended that no 'safe limit' existed. Frequency of consumption was considered more important.

Reviews of the literature

These are various approaches to locating, appraising and synthesizing evidence from scientific studies in order to obtain a reliable overview, becoming invaluable with the wealth of information that is available today. Dentistry is dealing with huge amounts of information on a regular basis and in order to utilize the salient literature produced, and literature systematic reviews are appearing more often (13). Mulrow (15) reported on the rationale for reviews by exploring their use as an efficient scientific technique, avoiding the cost and time expenditure of carrying out a new study (16).

Studies on sugar–caries

There have been many reports on the effects of sugars on dental caries incidence, each using different methods of dietary analysis. Food frequency questionnaires make up a substantial proportion of these methods and are used for assessment where sample sizes are large. Twenty-four hour recall and diet histories are also commonly represented in the literature and assessment has been determined by both interviews and questionnaires. No universal standardized methods for caries assessment have been reported to date, but the most regularly used diagnostic criteria are those presented by the WHO (17), Radike (18) and BASCoD (16). Even though standardized criteria may be reported, the caries index measured may vary so that differences between investigations are difficult to compare.

Sugar–caries relationships

An exact relationship between consumption of sugars either as quantity or frequency and caries still remains unclear. Established theories have long blamed sugar as the most important aetiological factor (12); however, the quality of such study designs has come under question. With this large quantity of varied data relating caries and sugar consumption it is important, nevertheless, not to lose sight of the multi-factorial nature of the disease process and how disease levels have changed. Caries and sugar consumption in the 21st century no longer represents a linear relationship, as poor correlations between total sugar consumption and caries prevalence, within communities are

now being reported (19). It is, however, still recommended that restriction of sugar consumption is considered a major caries-preventive measure, but the use of fluorides, education and oral hygiene are confounding practices and play more important roles.

A study was designed to review the evidence from the dental literature concerning the claim that sugar (sucrose) was the main aetiological agent in dental caries.

Materials and methods

The collection and categorization of papers was carried out with a view to extracting reliable data for analysis. This was achieved by categorizing relevant publications in the literature into groups: A (adequate, fulfilling all selection criteria), B (relevant but not fulfilling all selection criteria) and C (fulfilling less than half of the selection criteria). An overview was used to analyse the results to produce a more precise estimate once manuscript selection had been covered.

The review began with a protocol to incorporate the following agenda

- formulation of the question;
- location and selection of relevant studies;
- quality assessment of the studies involving critical appraisal;
- data collection where appropriate;
- analysis and presentation of the results.

The protocol for the review was based on the guidelines outlined in the Cochrane Handbook, normally used for randomized controlled trials. However, for the specific purposes of this review techniques and selection criteria were modified and adapted for the type of papers that were to be reviewed. A set of criteria was then developed specific to assess the relationship of sugar quantity or frequency of use to dental caries in humans (Table 1).

Populations

As dental caries affects all ages, all studies with varying age groups were considered for the review, with the exclusion of those reports that pertained to elderly populations (>65 years) or physically and mentally disabled. Caries in this older age group and in adult populations generally differs from children and adolescents, in that adults exhibit coronal and root surface caries (20). Also the majority of new carious lesions in the adult population are recurrent caries, requiring replacement restorations, unlike dental caries in children, which is usually coronal caries only. Because of this, older age groups, i.e. >35 years of age, were excluded. There were a number of papers that focussed on early childhood or nursing caries (ECC), but in all cases the diet analyses concerned pre-weaning drinks and are diffi-

Table 1 Selection criteria used in a literature search on sugar and dental caries

Study characteristics	
1.	Was there comparability of groups at baseline and adjustment for confounding factors?
2.	Was the sample properly stratified, the basis of selection recorded or was it a convenience sample?
3.	Were there clear inclusion/exclusion criteria and a record of dropouts?
4.	Were subject characteristics: age, gender or special group (students) recorded?
5.	Was the duration of follow-up a minimum of 2 years?
6.	Was type of diet(s), duration of use or dietary instructions recorded?
7.	Were diet diaries used and were data on diet collected daily, weekly or monthly?
8.	Was dietary assessment recorded by interview or self-completed questionnaire?
9.	Was sucrose (sugar) consumption recorded: quantity (how measured) and/or frequency?
10.	Was the form of sucrose used recorded: sugar, snacks, soft drinks, juices etc.?
Outcome characteristics	
11.	Was reproducibility of caries data assessed and a blind outcome assessment?
12.	What was the method of caries data collection described: visual, radiographic or both?
13.	Were teeth for caries examination dried/cleaned, and was an artificial dental light used?
14.	Was the diagnostic criterion for caries an accepted one (WHO, BASCoD, Radike, NIDR etc.)?
15.	Was there calibration/training of examiner and was inter- and intra-examiner reliability reported?
Other criteria	
16.	Was there a power calculation of <i>a priori</i> calculation of sample size?
17.	Were valid statistical tests used in the assessment of outcome?
18.	Was it stated that consent (informed) obtained?
19.	Was sponsorship of the trial(s) recorded?
20.	Was the population status at initiation recorded?
21.	Was background fluoride use (drops, tablets, etc.), artificial/natural water fluoridation recorded?
22.	Was there an overall outcome of the study recorded?
23.	Was it published in a recognized peer-reviewed journal?

cult to interpret. Accordingly, studies for inclusion were restricted to those with children over 4 years of age. Where studies covered a range of childhood, such as 2–8 years, and it was difficult to exclude the data for the pre-school children, who might not have been weaned, these studies were set aside.

Where possible, data were extracted for different age subgroups. Each was then recorded, analysed and collated separately in order to provide more useful results, pertinent to all stages of dental development. Populations from all countries were considered, including ethnic minorities within a particular region and comprised both men and women as long as the full publications were in English. Records were made of ethnicity and reference to a special

group was also noted, for example, dental students or clients in mental health institutions. However, all papers had to have been published in peer-reviewed journals. This excluded government published reports (21) that appear never to have been published under peer review conditions.

Exposures to sucrose or interventions

Only exposures or interventions that were associated with the use of sucrose in the diet, both qualitatively and quantitatively, were collected for inclusion. This meant the selective use of the disaccharide, sucrose in its many forms, including sucrose-based carbonated soft drinks, baked goods, sweets and table sugar, as added to other foods and drinks. Sucrose exposures were also collected on a group and individual basis. In some situations, data for National Consumption of sugar were collected as it was felt to be relevant. Studies using dental caries and sugar data from many countries for inter-country statistical comparison were set aside.

Outcome measure

The disease process of importance and the primary outcome measure were determined to be *dental caries experience*, measured as average caries levels across populations, where cross-sectional data were used, and caries increments, where longitudinal data were used. Caries was recorded for coronal lesions only and involved diagnosis at one or more of the levels, including visual, radiographic, radiographic and visual, or tactile. Caries diagnoses for either a single tooth or tooth surfaces were considered appropriate as long as established criteria had been used (16–18). In addition, the actual methods of caries examinations needed to be described, such as were the teeth dried, cleaned and was natural or artificial lighting used?

Location and selection of relevant studies

Identification of reports, only those published in English, was carried out by hand searching from 1856 to 1966 and then from 1966 to June 2007 included both hand and electronic database searching. Hand searching often involved location of archived papers by identification from Index Medicus and Index to Dental Literature, with the emphasis on the latter, and then searching the relevant early publications located in the University of Leeds Library's antiquarian collection.

The search for 1966–2001 involved the use of the electronic databases. The title and abstract were viewed for each article and determined if the paper would meet the

predetermined eligibility criteria. If in doubt, the full text of an article was obtained, checked, and if invalid – rejected. Where there was still doubt relating to the validity of a paper it was selected and included in the critical appraisal as early rejection might have resulted in loss of important studies, later valid, when stringent criteria had been applied. Identification of reports was through electronic searches of the databases: MEDLINE and EMBASE. These were initially searched independently, although the facility to search simultaneously is now available. Assistance in selection of terms and methodology of database searching was obtained from the Research Department at Community Health, Sheffield NHS Trust. The following free text search strategy was used and applied to MEDLINE and EMBASE databases:

Dental caries	Caries	Decay	Cavity
Diet	Sugar	Sucrose	

Epidemiology

DMF/dmf with the use of Explode 'Dental Caries'/All subheadings

Explode 'Diet'/subheading cariogenic

In order to obtain more appropriate, refined results and for the avoidance of retrieving thousands of returns, the search parameters – *dental caries*, *caries*, *DMF*, *dmf*, *cavity and decay*, were linked with interventions, *sucrose*, *sugar*, *diet* and *epidemiology* by the use of Boolean operators (AND, OR). Spelling variations and truncations were handled using specific database wild card characters such as *cavit**, *diet**, with an asterisk or Dollar (\$). The search was narrowed to publications in English and to reports on humans. Electronic searching was only possible from 1966. A preliminary scan of other databases revealed no further references and detailed searching of such was therefore not carried out.

In many papers the type of dietary sugars studied or reported on was confusing. Thus some used milk-drinking with sugars possibly added, others fruit-eating or use of fruit juices. But these foods include complex sugars other than sucrose. These papers were set aside. In addition, there were some papers that assessed artificial sweeteners in addition to sugars and these were not considered principally because these studies were to assess the effect of artificial sweeteners and not for the relationship of sugar to caries. Finally, a few very recent papers assessed the use of intrinsic, non-milk extrinsic sugars or extrinsic sugars, which would have complicated the paradigm and were also not considered. Accordingly, only reports on 'free-sugars' were used.

Hand searching key journals, which had not already been searched by MEDLINE or EMBASE, were also carried out using the Index to Dental Literature and to a lesser extent Index Medicus. It has been estimated that only between 30% and 80% of relevant reports are located with

MEDLINE and EMBASE, and it was therefore found necessary to hand search for key journals (22). Searching Index Medicus and Index to Dental Literature used the subject categories and titles of dental caries and diet, dental caries and carbohydrates and epidemiology. Hand searching was commenced in 1856 using Dental Cosmos and British Journal of Dental Science and then available journals until 1940 as a general search and then post 1940 as a detailed search, as caries diagnosis before this time could not be relied upon to be sufficiently accurate for inclusion in the review. Methods of caries diagnosis have been in existence since the mid-1800s (23), but there had been no systematic methodology described in the literature until the publications of Bodecker (24). Through the period from 1940 to 2001 subject headings in the dental literature changed and were accounted for accordingly.

From the initial list of retrieved articles the references were checked from one to another, utilizing a technique known as *pearling*, the ancestry approach or citation chasing. This involves checking reference lists of retrieved manuscripts, and continuing until a point was reached where citation checking revealed few or no further relevant studies. Finally, a cut-off date of 30 June 2007 was set, beyond which no further searches were carried out.

Filtering of the literature

Once selection of the relevant papers had been accomplished, all appropriate and useful studies were photocopied from the Medical Library at the University of Leeds or ordered from the British Dental Association Library. This was carried out for the majority of manuscripts, although some were obtained through inter library loan. Selection relied upon scrupulous examination of the studies to determine the relevance and quality of the publications, and clearly irrelevant papers were discarded. From an initial search on the electronic database and hand searching, the references from those studies identified to 2007 were checked and all further papers identified and followed up.

Quality assessment of the studies including critical appraisal

Application of the 23 selection criteria (Table 1) was carried out with attention paid to types of study, participants, intervention characteristics and outcome measures collected. A database was designed, using 'Reference Manager' to hold a catalogue of all identified papers. This was to allow the reviewers the ability to cross-check for any duplicated or repeated studies.

Methods of the review

Two reviewers (CAA, MEJC) checked all titles and abstracts identified through the searches both electronic and by hand. Full texts of all studies of possible relevance for independent assessment were obtained. It was impossible to 'blind' the journals for this review, although this is often carried out to eliminate bias where the reviewer may already be familiar with other authors' work in the field. Without retyping and omitting vast amounts of detail from the collected articles it was not possible to blind the reviewers to the work carried out on caries and sugar consumption over the past few decades. After having read the papers, the reviewers met to assess their findings and to establish which trials or reports fitted the selection criteria, and graded their methodological quality. Any disagreement was resolved by discussion between the reviewers. The methodological quality of the included reports collected, with particular emphasis on the selection criteria, was ranked using the following approach:

Grade A: Adequate fulfilling all selection criteria

Grade B1: Relevant and fulfilling at least 19 of the selection criteria

Grade B2: Relevant and fulfilling between 12 and 18 of the selection criteria

Those papers that fulfilled 11 or less of the selection criteria were not placed in the final assessment, set aside and recorded as Grade C.

Each paper was carefully studied and methodological application of the selection criteria carried out. Retrieved studies were considered and an updated record maintained of the overall grade for each manuscript in the Reference Manager database. It was through discussion between the reviewers and attention to previously published reviews (25) that the selection criteria were established. The following selection criteria were applied to each of the retrieved manuscripts in the following manner. Each criterion was weighted the same. The selection criteria were divided into the following categories.

Study group characteristics

For each of the selection criterion, a statement, relative to the determinant applied, was recorded. Where a final data analysis was not recorded, for either quantity or frequency, this was recorded as not applicable (N/A). Agreement on methodology assessment was by using kappa statistics, carried out by re-examining a random selection of papers at the end of the appraisal process. After thorough scrutiny, all papers coded A, fulfilling all the criteria or B1, fulfilling at least 19 of the criteria were then included for the subsequent analysis and entered onto a separate database for ease of identification and data pertaining to the overall

outcome measure recoded. The primary reviewer (CAA) performed data extraction independently for included papers. Statistical accuracy was determined with help of qualified medical statisticians, and it was at this stage that the likelihood of carrying out a *meta-analysis* was deemed inappropriate and a decision made to use a *systematic review*. Statistical pooling of data to provide an overall estimate was not possible as that collected was so varied.

Results

The results from the hand searching provided no useful studies prior to 1940 and therefore they are not listed in the references. These early reports, such as that of Pederson (9), did not meet any or very few criteria. The post 1940 search identified some useful studies not entered under the standard headings for Medical Subject Headings (MeSH) terms on the MEDLINE and EMBASE databases, as allocation to specific MeSH terms is subject to human error and misinterpretation in categorizing. Following the first hand and electronic searching, the total number of papers identified for further detailed checking was in the hundreds.

Search from 1940 to 1966

Hand searching the period from 1940 to 1966 provided 23 reports unidentified in the electronic search. After checking, it was found that only 5 of the 23 reports found were suitable for inclusion in the critical appraisal and the other 18 papers were eliminated altogether or photocopied for information only, where they contained information of future interest. Again, these papers were published at a time when there were no accepted protocols for such studies. Each and every paper is different, making comparisons impossible.

Hand searching from 1966 to 2007

The results from this period provided a further 35 papers for submission to the appraisal section. These papers were cross-checked with the electronic database collection to eliminate any duplicates.

Citation chasing

Reference lists from previously selected papers were cross-checked against the database of entries providing a further 13 papers for inclusion. After complete filtering of the literature, provided by reviewing the titles and abstracts of the papers retrieved from the electronic database and hand searching, a total of 91 papers were included in the final appraisal. Papers up to this stage of the research were discarded for various reasons, including those that had no specific caries data related to sugar consumption, were

review papers, government reports, studies on ECC or artificial sweeteners, or reports where the data had already been presented in a previous study.

Intra-reviewer reliability

A subgroup of 15 of the papers was examined twice. There was total agreement in the overall code for each paper between the first and second readings and a kappa score could not be calculated.

Grading of papers

Results using the predetermined selection criteria provided only one paper that fulfilled all the determinants, Grade A. There were 30 papers graded B1, fulfilling at least 19 of the selection criteria. All other papers (64) were graded either B2 or C, and are shown in Table 2, with an indication as which of the selection criteria were not met. These papers were not considered further in the review.

An 'A' paper (26) gave data on a cross-sectional study carried out on a population of Spanish school children aged 5–15 years old. Dietary assessment was calculated from a food frequency questionnaire containing 44 items, including sugar-containing and sugar substitute foods. The overall estimate showed that pastry was the food item associated with the highest relative risk of caries, (odds ratio = 3.02; CI 1.51–6.05), and that consumption of ice cream, cakes and sliced bread also showed a positive relationship with dental caries. A protective effect of two other foods consumed, (skimmed milk and artificial sweeteners) was found, but the use of sugar-free gum and candies was positively correlated with caries.

A number of papers were concerned with early childhood caries or nursing caries. These studies all used very young infants where caries diagnosis is fraught with difficulties and reproducibility. In addition, dietary assessments are also unreliable. Accordingly, these papers were set aside. Similarly, papers taking a global view and using data from many different sources were also set aside. However, these papers are listed in Table 2 for completeness.

Finally, the papers that were included in the review are listed in Table 3. This shows whether there was or was not any statistically significant relationship reported, in each paper, for caries related to sugar quantity or frequency of use. If no assessment was reported in a paper, on either quantity or frequency, this is shown as N/A.

Discussion

This literature review revealed that few papers over the past 150 years or more met the necessary criteria for modern assessment. It was also surprising that some of the so-called classic studies (10,11) were not able to be included. This no

Table 2 Papers not included in the final analysis and graded B2 or C

Ahmed *et al.* (2007) (3,5–7,11–13,15,16,21,22)
 Akpata *et al.* (1992) (1,3,5,10,12–14,16,18,20–22)
 Bagramian and Russell (1973) (5,7,9,14–16,20)
 Bagramian *et al.* (1974) (1,3,5,11,13–16,18)
 Birkhed *et al.* (1989) (1–3,5,11–16,19,21)
 Burt and Szpunar (1994) (1–3,5,11,13,15,16,18–20)
 Clancy *et al.* (1977) (1–3,5,11–16,19,21,22)
 Duany *et al.* (1972) (1–3,5,11–16,18–22)
 Gustaffson *et al.* (1954) (1–3,12–14,16,18)
 Hankin *et al.* (1973) (1,3,5,11–16,19,20,22)
 Hargreaves (1972) (1,5,11–13,15,16,20–22)
 Hausen *et al.* (1981) (3,5,7,9,11–16,18,19,21)
 Holbrook *et al.* (1995) (1,3,5,6,9–16,20,22)
 Hollund (1987) (1,3,5,6,9,10,12–16,22)
 Jamel *et al.* (1997) (1,3,5,6,7,9,16,18,19,20–22)
 Johnsen *et al.* (1980) (1,5,9,11–16,22)
 Kalsbeek and Verrips (1994) (3,5,9,10,14–16,20)
 Kerosuo and Honkala (1991) (3,5–7,9,13,16,21,22)
 Kuusela *et al.* (1997) (1–3,6–9,11–16,18–22)
 Lachapelle *et al.* (1990) (1–3,5,14,16,18,22)
 Levine *et al.* (2007) (1,2,11,13,15,16)
 Marques and Messer (1992) (1,5,14,16,19)
 Marshall *et al.* (2005) (1,3,13,14,16,22)
 Martinsson (1972) (1,5,6,7,9,11–16,19–22)
 Neiderud *et al.* (1991) (2,5,6,11,13–16,22)
 Normark (1993) (1,3,5,7,9,10,13,14,16,18–22)
 Petridou *et al.* (1996) (1–3,5,10,11,13,15,16,19–22)
 Retief *et al.* (1975) (1,3,5,11,13–16,18–22)
 Richardson *et al.* (1977) (1,3,5,11–16,18–22)
 Richardson *et al.* (1978) (3,5,11–14,16,18,20–22)
 Sahoo *et al.* (1992) (1–3,5,7,9,13,14,16,18,19–23)
 Sgan-Cohen and Katznelson (1988) (1,3,5,11,13–16,18,19,21,22)
 Steyn *et al.* (1987) (1,3,5,13,16,18–22)
 Sundin (1990) (1,3,7,9,11,13–16,22)
 Szpunar *et al.* (1995) (3,11,13,15,16,18,22)
 Takahashi (1961) (1,3,5–16,18,19,21,22)
 Takuechi (1960) (1,2,5,6–15,16,18–22)
 Tubert-Jeannin *et al.* (1994) (1,3,5,9,11–16,18–22)
 Walker *et al.* (1980) (2,3,5,11,13–16,18,19,22)
 Wilson and Ashley (1989) (1,2,3,8,10,13–16,18,20–22)
 Yabao *et al.* (2005) (1,3–5,11–13,16,20–22)
 Zita *et al.* (1959) (1–3,5,11,13–16,18,19,21,22)

Other papers:

Early childhood caries:

- Gibson and Williams (1999)
- Gordon and Reddy (1985)
- Gryten *et al.* (1988)
- Hinds and Gregory (1995)
- Sakuma *et al.* (2007)
- Sgan-Cohen and Salinger (1982)
- Sgan-Cohen *et al.* (1984)
- Silver (1987)
- Stecksen-Blicks and Borssen (1999)
- Tsai *et al.* (2006)
- Van Pallenstein-Helderman *et al.* (2006)
- Wendt and Birkhed (1995)

Adults, farmers, sweeteners, etc.:

- Glass and Fleisch (1974) (Breakfast cereals)
- Cleaton-Jones *et al.* (1987) (No caries data)
- Garn *et al.* (1979) (Review paper)
- Granath *et al.* (1978) (OHI and Fluoride)
- Grobler (1991) (Fruit farmers)
- Maslin *et al.* (1994) (Older adults)
- Reekola (1987) (Sweeteners)
- Walker (1975) (Review paper)

Between countries:

- Kuusela *et al.* (1999) (Between countries)
- Sreebny (1982) (Global data)

The selection criteria on the basis of which each paper was not included is listed (see Table 1).

doubt reflects changing ideas on scientific standards. One paper, the milestone study referred to as the Vipeholm Study (12), was assessed just in the grading review but with an insufficient score to be included in the final analysis.

A comparison can be made with another recent attempt to complete a systematic review of sugar consumption and caries risk by Burt *et al.* (25). Their conclusion was that the relationship between sugar consumption and caries is much weaker in the modern age of fluoride exposure. The approach taken by Burt *et al.* (25) was to use a point-scoring system to assess each paper published only after 1980 and before 2000. Differential scores were given to add weight to such entities as ‘clearly stated aims’ and ‘confounders accounted for’. Their literature selection gave 809 papers reduced on first assessment to 134 that was then reduced on using inclusion/exclusion criteria to 69. On the basis of the paper’s scores of at least 55 points out of a maximum of 100, their final list was 36 papers compared with 31 here.

Comparing the final lists of this study with that of Burt *et al.* (25), 19 of their papers, (scoring 55 points or more) appear in our list, indicated by ‘*’ in Table 1. On the other hand, 26 of our papers appear in Burt *et al.*’s list (25). The difference lies in the selection criteria used. This is not surprising as the two approaches to selection were different but equally valid. For example, this previous review (25) included root caries whereas we did not. The only paper graded A in the present study (26) appears in the list of this previous review (27). In discussing the outcome of the two literature reviews by ourselves and Burt *et al.* (25), a number of factors are pertinent.

Power calculation/a priori

The importance of a predetermined power calculation has already been noted above. For all the papers in the B1 category, except one (27), this either had not been carried out or was not stated in the text of the report. The advantage of increased power is particularly relevant to conditions of relatively low event rates or when small effects are being assessed. In considering the outcome measure, *dental caries*, this is neither an uncommon event nor the effect to be studied small. This situation might occur where reference to caries levels of less than one surface over a period of 2 years or more is stated. It was, therefore, reasonable to include these papers for the overall review. A large sample size increases the statistical power but may produce a result that would have little or no clinical significance. Sample sizes studied and used for the analysis in the review varied from $n = 69$ (28) to $n = 139$ (29). Results from the B1 papers with very large or small samples must be interpreted with caution, for the reasons previously mentioned.

Study (year) (reference number)	Significant relationship: total sugar consumption	Significant relationship: frequency of sugar consumption
Angelillo <i>et al.</i> (1999)* (41)	N/A	X
Árnadóttir <i>et al.</i> (1998)*	NS	X
Beighton <i>et al.</i> (1996)*	NS	X
Bjarnason <i>et al.</i> (1989) (31)	N/A	X
Burt <i>et al.</i> (1988)* (38)	X	NS
Cleaton-Jones <i>et al.</i> (1984a)	NS	NS
Cleaton-Jones <i>et al.</i> (1984) (36)	NS	NS
Creedon and O'Mullane (2000)	N/A	X
Freeman <i>et al.</i> (1997)*	N/A	X
Garcia-Closas <i>et al.</i> (1997)* (42)	N/A	NS
Grindefjord <i>et al.</i> (1995)*	N/A	X
Grindefjord <i>et al.</i> (1996)*	N/A	X
Larsson <i>et al.</i> (1992)	NS	NS
Holbrook <i>et al.</i> (1989)	N/A	X
Holbrook <i>et al.</i> (1993)* (32)	N/A	X
Holt (1991)*	N/A	X
Ismail (1986)* (29)	X	X
Karjalainen <i>et al.</i> (2001)*	X	X
Kleemola-Kujala <i>et al.</i> (1979) (35)	X	X
Mazengo <i>et al.</i> (1996) (37)	NS	X
McMahon <i>et al.</i> (1993) (39)	NS	NS
Petti <i>et al.</i> (1997)* (33)	N/A	X
Rodrigues and Sheiham (2000)* (27)	X	X
Rugg-Gunn <i>et al.</i> (1984)*	X	X
Sampaio <i>et al.</i> (2000)	NS	NS
Serra-Majem <i>et al.</i> (1993)* (26)	N/A	X
Sgan-Cohen <i>et al.</i> (1984)	N/A	NS
Stecksén-Blicks <i>et al.</i> (1985)*	N/A	NS
Stecksén-Blicks and Holm (1989)	N/A	NS
Sundin <i>et al.</i> (1983)* (30)	NS	NS
Sundin <i>et al.</i> (1992)*	N/A	NS

*Included in Burt *et al.* (2001) with 55 points.

Bold: Grade A paper.

NA, not applicable; NS, no significant relationship identified; X, significant relationship identified.

Table 3 Summary of reports graded A or B1 included in a review of the literature on any relationship between sugar and dental caries as quantity and/or frequency

Blind outcome assessment

Each paper categorized as B1 provided satisfactory data to enable the reader to determine if the caries assessment made was carried out in a blind manner. This was either stated in the presented literature or conditions were described as such that the assessment could only have been carried out in this manner. Examples of this, referred to in the text of the reports, include the assessment of the dietary intake by personnel other than the examining officers at a time, after, or remote from the clinical examination.

Adjustment for confounders

This criterion was given a high potential score by Burt *et al.* (25) to emphasize the importance of potential confounders to alter the results. Variation in adjustment for confounders was widespread across the manuscripts collected and subsequently appraised. The effects of such

varied adjustment make comparisons between studies difficult, especially if multiple confounders were accounted for in the statistical analysis for some reports and not in others. All papers coded B1, except one (30) adjusted for some confounders in the results section published and statistics used included multivariate logistic regression. The major adjustments reported in the individual studies included assessment for confounders of *sex, age, tooth-brushing habits, dental health education and background fluoride water levels*. The diverse conduct and lack of homogeneity between studies further stress the multifactorial nature of the caries process, and results are to be interpreted with this in mind.

The effects of salivary counts of *Streptococcus mutans*, where high levels are known to be associated with the cariogenicity of carbohydrates, have also been studied (31). It was reported that the consumption of sweetened baked goods might be a determinant of caries prevalence in children with moderate to high levels of salivary *S. mutans*,

(odds ratio = 6.1, 95% CI: 1.6–23.0). Holbrook *et al.* (32) also studied the effects of *S. mutans* and lactobacilli counts and introduced other salivary factors, including salivary flow rate and pH. ‘Misuse’ of sugar (more than seven exposures per day) was reported to be the most significant factor when predicting caries (odds ratio = 6.46), and salivary pH and flow rates were less important.

Inclusion/exclusion criteria

All papers appraised and graded B1 reported clearly described inclusion and exclusion criteria. Manuscripts were included, as they were also by Burt *et al.* (25), where details relating to the nature of the sample were suitably provided including the sampling technique and the reported numbers of dropouts. Studies also provided numbers and percentages of participants that had completed well-documented dietary assessments by either interview or questionnaire. Substitution for dropouts was considered inappropriate and studies using this technique were not included. Some 28 papers used convenience samples of either school children, or those attending pre-school nurseries. Families were invited to participate in the studies and provide dietary information.

Other papers described samples, such as 18-year-old male army recruits (29,33), used data for individuals from the first National Health and Nutrition Exam Survey (NHANES I). Criteria for inclusion in the report involved sampling those participants with high caries levels, above or equal to the 80th percentile, and those with low caries levels, less than or equal to the 20th percentile. The ubiquitous nature of dental caries enables studies of the disease to be carried out across all age groups, and as already described; most participants used for inclusion in caries assessment were from groups of children attending schools. This method of selection provides a convenient sample of easily obtainable recruits in readily available settings for examination and interview.

Duration of studies

Nine of the B1 papers were longitudinal in design and the duration of these studies ranged from a minimum of 1 year to a maximum of 3 years. After careful consideration, those reports of 1-year duration (27,31) were included as all other selection criteria had been adequately fulfilled or where the study related to caries in the primary dentition. This was considered appropriate, as caries progression in this age group has been documented as being more rapid than in the permanent dentition (34). All other case-control or cohort studies presented data from studies with 2 years minimum duration.

Age of study groups and if they were special groups

The variation in age groups ranged from 1 to 74 years in the studies within the dental literature but for this analysis only those groups <35 years old were included. In one study caries was reported for 18-year-olds only (35), whereas all other B1 papers presented data for children either in isolation or with some data for adults. The primary dentition was studied in 15 of the reports and the permanent teeth evaluated in adolescents in 16 of the studies.

Caries and dietary assessments were carried out on the permanent dentitions of adults in four papers, where the adults were classed as being over 18 years and over. One paper summarized data for the primary and permanent dentitions (35) using dmfs and DMFS scores. Special groups were noted in three papers (33,36,37) and represented an ethnic minority of Indians in South Africa, farm workers from citrus and cereal farms, and Sardinian army recruits.

Calibration of examiners

Calibration of examiners, noted as ‘examiner reliability quantified’ (38), is an essential component of caries diagnosis and only those studies where this was carried out were given full recognition as being of sufficient quality to be graded B1. McMahon and co-workers (39) did not state in their published manuscript if clinical examiners were calibrated and to what level. The paper was, however, included as WHO (17) criteria that were used for caries assessment, which requires examiner calibration. All other papers, where one examiner carried out the clinical examinations, recorded a minimum intra-examiner reliability of 70% agreement and where more than one examiner was used; inter-examiner reliability of more than 70% was recorded. Some of the papers graded B2 mentioned that examiners were trained and calibrated but, however, gave no further details as to how reliable were the examiners; kappa scores were not given.

Sponsors of trials and publication status

Sponsorship of studies could be important because of any question of bias. However, this analysis showed that Dental societies, Government and Departments of Health funded most studies. Only two papers in the review were sponsorship by industry (40,41).

Publication status

This was where the name of the journal used to publish the data was considered as the status of the journal could be

important. In all, 12 different journals were used for publication of the reports and all were found to be well recognized and refereed journals. Presentation of manuscripts fulfilling the requirements for B1 category was all published post 1979. Many papers prior to this date were rejected for various deficiencies. Those papers were not of sufficient quality to be considered in the review, and many of the reports, although clearly relevant, were carried out prior to the 1980s when standards of review and selection by journals might not have been as exact. This meant that many older papers did not fit the criteria commonly accepted for modern day systematic reviews and meta-analyses.

Rural/urban community and background water fluoride level

There were 22 urban settings, 3 rural and 5 where the data were collected from both urban and rural populations. None appeared to have any relevance to the final assessment. Water fluoride levels were recorded for 17 areas in the published manuscripts and no stated level for the other 14 publications. Fluoride levels varied from <0.1 p.p.m. to 1 p.p.m., the optimal level. Background fluoride levels obviously have a bearing on any relationship of sugar consumption and caries prevalence, and it has been noted that the relationship becomes less important where adequate levels of fluoride use are in place (27).

Dietary intake

The methods used for the assessment of dietary intake were diverse and do not relate solely to analysis of sugar as sucrose, or as mono- or disaccharides. References, which include sucrose containing foods e.g. sweets, candies, cakes and beverages, were also included. It should be noted that sucrose containing foods and beverages supply a range of other nutrients, which may be implicated in caries aetiology. In general, the lack of consistency in the methods of dietary analysis hampered the interpretation of the results.

There were 15 papers graded B1, reporting a total quantity of sucrose as measured in gm d^{-1} , one paper stated gm of sucrose consumed per 1000 kcal consumed (35), and one paper stated quantities of sucrose as *large*, *moderate* and *small* amounts (28). All other manuscripts did not assess total sugar consumption, and this was recorded in Table 3 as NA (not applicable). The paper graded A did not state a total sugar consumption.

Frequency of consumption was reported in all of the B1 papers; however, the lack of consistency regarding the frequency variables measured made comparisons of studies difficult. Frequencies were variously reported as

- between meal consumption (snack frequency);
- total frequency of eating episodes throughout the day;

- at and between meals intakes of sucrose (total frequency throughout the day);
- weekly frequency of total sugars;
- weekly frequency of snack and sweet intakes;
- other variables relating to specific food groups.

It was this area of the analysis that caused the greatest difficulty in assessment because of the lack of consistency. The approaches taken were many and varied making comparisons very difficult. This was also reported previously (27) and there obviously needs to be greater agreement among dental researchers in the future for any similar studies as to how frequency of sugar use should be measured.

Caries measurement and diagnostic criteria

These measurements were reported as visual, tactile and radiographic assessments. Details of methods used were well reported in the materials and methods section of each manuscript and all but six papers used predetermined tested diagnostic criteria. White spot lesions and early arrested caries were generally not included in statistical analysis, but where this was carried out reference to the inclusion of incipient lesions was clearly documented. Caries increments were recorded for the longitudinal studies and papers reported both single tooth measures and tooth surface measures, for primary and permanent teeth. In all there was little in-the-way discrepancies between caries diagnostic methods. This is probably because the criteria for caries diagnosis has been well established for many years and there is, by and large, agreement.

Statistical measures and main outcome

This was ideally expressed as a relative risk or odds ratio. Where this was not possible the main outcome was expressed as comparisons between means that were statistically significant at the 5% level. Positive results in Table 3 are recorded as X and where tests were not carried out on a variable this is stated as N/A. This is important when analysing the results, as 16 reports did not contain data pertaining to the total consumption of sugar. A summary of the statistical results is presented in Table 3. Only 6 of the 15 papers reporting on quantity of sugar to caries found a significant relationship, but many others did not apparently look. However, for frequency of use the outcome of the systematic review shows a significant relationship with 19 out of the 32 reporting caries related to frequency. This could not be considered an overwhelming relationship and should be described perhaps as significant but moderate.

Sugars, diet and caries

Finally, it must be pointed out that only extremely rarely is sugar consumed on its own, but as part of a food. It is

interesting that several studies made note of the relationship of caries to baked goods. When refined sugar became widely available in the 19th century it did so at the same time as the mass production of white flour, which is high in gluten and enables pastry and baked goods, such as biscuits, to become widely available or made at home. Over the years, a number of authors have questioned the perceived opinion that sugar is directly related to dental caries (42) and noted that the precise responsibility of sugar to caries was controversial. Earlier Bibby (43) asked whether we told the truth about caries, and its direct relationship to sugars and later the same author (42,44), discussed this problem extensively pointing out that dental caries prevalence in the USA was related more significantly to the use of baked goods and not to sugar per se. More recently (42), it has been found that the consumption of sweetened baked goods was significantly related to caries. The rapid rise in dental caries prevalence in the 19th century has been related to the industrial manufacture and wide availability of sugar; however, the same claim can be made for white flour. It can be postulated that the lack of significant relationships of sugar to dental caries is because it is the frequent use of the white flour-sugar combination in baked goods (cakes, biscuits etc.) and snack foods that is the true relationship.

Conclusion

A review of the literature to determine any relationship between dental caries and sugar use has shown that only 31 papers of those published from 1856 to 2007 fulfilled the necessary inclusion criteria. The analysis showed that there is no reliable relationship of quantity of sugar used to dental caries. A significant relationship of frequency of use of sugar(s) to dental caries was reported in 19 out of the 31 papers considered.

Conflict of Interest Statement

All authors declare no conflicts of interests.

Acknowledgements

The authors wish to particularly thank Dr Andrew Blance of the Statistical Computing Centre, Nuffield Centre for Health Studies, University of Leeds, for his advice and interest in the conduct of this study. The work reported here was part of the Master of Dental Science degree in Paediatric Dentistry of the senior author at the University of Leeds and supported by departmental funds.

References

1. Allsop KA, Miller JB. Honey revisited: a reappraisal of honey in pre-industrial diets. *Br J Nutr* 1996; 75: 513–520.

2. Fauchard P. *Chirugen Dentiste*. Pierre-Jean Mariette: Paris, 1746.
3. Berdmore T. *A Treatise on the Disorders of the Teeth and Gums*. Dublin, 1769.
4. Miller WD. *The Microorganisms of the Human Mouth*. S.S.White: Philadelphia, PA, 1890.
5. Sheiham A. Why free sugars consumption should be below 15 kg per person per year in industrialised countries: the evidence. *Br Dent J* 1991; 171: 63–65.
6. COMA CoMAoF. Dietary sugars and human disease. Report of the Panel on dietary sugars. Report on Health and Social subjects. HMSO: London, 1989.
7. Hussein I, Pollard MA, Curzon MEJ. A comparison of the effects of some extrinsic and intrinsic sugars on dental plaque pH. *Int J Paediatr Dent* 1996; 6: 81–87.
8. Marsh P, Martin M. *Oral Microbiology*, 4th edn. Wright: Oxford, 1999.
9. Pedersen PO. *The East Greenland Eskimo Dentition*. Munksgaard: Copenhagen, 1932.
10. Harris R. Biology of the children of Hopwood House, Bowral Australia. 4. Observations on dental-caries experience extending over 5 years (1957–61). *J Dent Res* 1963; 42: 1387–1399.
11. Fisher FJ. A field study of dental caries, periodontal disease and enamel defects in Tristan da Cunha. Part 2. Methods and Results. *Br Dent J* 1968; 125: 447–453.
12. Gustaffson B, Quensel C-E, Swenander Lanke L, Lundqvist C, Grahnen H, Krasse B. The Vipeholm dental caries study. The effect of different levels of carbohydrate intake on caries activity in 436 individuals observed for five years. *Acta Odontol Scand* 1954; 11: 232–264.
13. Ismail AI, Bandekar RR. Fluoride supplements and fluorosis: a meta-analysis. *Community Dent Oral Epidemiol* 1999; 27: 48–56.
14. Cleaton-Jones P, Richardson BD, Sreebny LM, Fatti P, Walker AR. The relationship between the intake frequency and the total consumption of sucrose among four South African ethnic groups. *J Dent Child* 1987; 54: 251–254.
15. Mulrow CD. Rational for systematic reviews. *Br Med J* 1994; 309: 599.
16. Palmer JD, Anderson RJ, Downer MC. Guidelines for prevalence studies on dental caries. *Community Dental Health* 1983; 1: 55–66.
17. World Health Organisation. *Oral Health Surveys. Basic Methods*. WHO: Geneva, 1987.
18. Radike A. Criteria for diagnosis of dental caries. In: ADA (ed.). *Proceedings of the Conference on the Clinical Testing of Cariostatic Agents*. October 14–16, 1968. ADA Council on Dental Research: Chicago, IL, 1972, pp. 87–88.
19. Harel-Raviv M, Laskaris M, Chu S. Dental caries and sugar consumption into the 21st century. *Am J Dent* 1996; 9: 184–190.
20. MacEntee MI, Clark DC, Glick N. Predictors of caries in old age. *Gerodontol* 1993; 10: 90–97.
21. Hinds K, Gregory JR. *National Diet and Nutrition Survey. Children Aged 1.5 to 4.5*. HMSO: London, 1995.
22. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *Br Med J* 1994; 309: 1286–1291.
23. Magitot E. *Treatise on Dental Caries: Experimental and Therapeutic Investigations*. Houghton and Osgood: Boston, MA, 1878.
24. Bodecker F. The modified caries index. *J Am Dent Assoc* 1939; 26: 1453–1456.
25. Burt BA, Pai S, Satischandra P. Sugar consumption and caries risk: a systematic review. *J Dent Educ* 2001; 65: 1017–1023.

26. Serra-Majem L, Garcia-Closas R, Ramon J, Manau C, Cuenca E, Krasse B. Dietary habits and dental caries in a population of Spanish school children with low levels of caries experience. *Caries Res* 1993; 27: 488–494.
27. Rodrigues CS, Sheiham A. The relationship between dietary guidelines, sugar intake and caries in primary teeth in low income Brazilian 3-year-olds: a longitudinal study. *Int J Paediatr Dent* 2000; 10: 47–55.
28. Sundin B, Granath L. Sweets and other sugary foods tend to be the primary etiological factors in dental caries. *Scand J Dent Res* 1992; 100: 137–139.
29. Ismail AI. Food cariogenicity in Americans aged 9 to 29 years assessed in a national cross-sectional survey. 1871–74. *J Dent Res* 1986; 65: 1435–1440.
30. Sundin B, Birkhed D, Granath L. Is there not a strong relationship nowadays between caries and consumption of sweets? *Swed Dent J* 1983; 7: 103–108.
31. Bjarnason S, Finnbogason SY, Norén JG. Sugar consumption and caries experience in 12- and 13-year-old Icelandic children. *Acta Odontol Scand* 1989; 47: 315–321.
32. Holbrook WP, de Soet JJ, de Graff J. Prediction of dental caries in pre-school children. *Caries Res* 1993; 27: 424–430.
33. Petti S, Panfili P, Tarsitani G, Simonetti D'Arca A. Oral hygiene, sucrose consumption and dental caries prevalence in adolescent systemic fluoride non-users. *Community Dent Oral Epidemiol* 1997; 25: 334–336.
34. Murray JJ, Majid ZA. The prevalence and progression of approximal caries in the deciduous dentition in British children. *Br Dent J* 1978; 145: 161–164.
35. Kleemola-Kujala E, Rasanen L. Dietary pattern of Finnish children with low and high caries experience. *Community Dent Oral Epidemiol* 1979; 7: 199–205.
36. Cleaton-Jones P, Richardson BD, Winter GB, Sinwell RE, Rantsho JM, Jodaikin A. Dental caries and sucrose intake in five South African preschool groups. *Community Dent Oral Epidemiol* 1984; 12: 381–385.
37. Mazengo CM, Tenovuo J, Hausen H. Dental caries in relation to diet, saliva and cariogenic microorganisms in Tanzanians of selected age groups. *Community Dent Oral Epidemiol* 1996; 24: 169–174.
38. Burt BA, Ekland SA, Morgan KJ, Larkin FE, Guire KE, Brown LO, Weintraub JA. The effects of sugars intake and frequency of ingestion on dental caries increment in a three-year longitudinal study. *J Dent Res* 1988; 67: 1422–1429.
39. McMahon J, Parnell WR, Spears GFS. Diet and dental caries in preschool children. *Eur J Clin Nutr* 1993; 47: 794–802.
40. Gibson S, Williams S. Dental caries in pre-school children: associations with social class, tooth brushing habit and consumption of sugars and sugar-containing foods. Further analysis of data from the National Diet and Nutrition Survey of children aged 1.5–4.5 years. *Caries Res* 1999; 33: 101–113.
41. Angelillo IF, Torre I, Nobile CGA, Villari P. Caries and fluorosis prevalence in communities with different concentrations of fluoride in the water. *Caries Res* 1999; 33: 114–122.
42. Garcia-Closas R, Garcia-Closas M, Serra-Majem L. A cross sectional study of dental caries, intake of confectionary and foods rich in starch and sugars, and salivary counts of *Streptococcus mutans* in children in Spain. *Am J Clin Nutr* 1997; 66: 1257–1263.
43. Bibby B. Do we tell the truth about preventing caries? *J Dent Child* 1966; 33: 269–279.
44. Bibby B. The cariogenicity of snack foods and confections. *J Am Dent Assoc* 1975; 90: 121–132.

Papers assessed and graded A or B1

- Angelillo IF, Torre I, Nobile CGA, Villari P. Caries and fluorosis prevalence in communities with different concentrations of fluoride in the water. *Caries Res* 1999; 33: 114–122.
- Árnadóttir IB, Rozier RG, Saemundsson SR, Sigurjóns H, Holbrook WP. Approximal caries and sugar consumption in Icelandic teenagers. *Community Dent Oral Epidemiol* 1998; 26: 115–121.
- Beighton D, Adamson A, Rugg-Gunn A. Associations between dietary intake, dental caries experience and salivary bacterial levels in 12-year-old English school children. *Arch Oral Biol* 1996; 41: 271–280.
- Bjarnason S, Finnbogason SY, Noren JG. Sugar consumption and caries experience in 12- and 13-year-old Icelandic children. *Acta Odontol Scand* 1989; 47: 315–321.
- Burt BA, Ekland SA, Morgan KJ, Larkin FE, Guire KE, Brown LO, Weintraub JA. The effects of sugars intake and frequency of ingestion on dental caries increment in a three-year longitudinal study. *J Dent Res* 1988; 67: 1422–1429.
- Cleaton-Jones P, Richardson BD, Sinwell RE, Rantsho JM, Granath L. Dental caries, sucrose intake and oral hygiene in 5-year-old South African Indian children. *Caries Res* 1984a; 18: 472–477.
- Cleaton-Jones P, Richardson BD, Winter GB, Sinwell RE, Rantsho JM, Jodaikin A. Dental caries and sucrose intake in five South African preschool groups. *Community Dent Oral Epidemiol* 1984; 12: 381–385.
- Creedon MI, O'Mullane DM. Factors affecting caries levels amongst 5-year-old children in County Kerry, Ireland. *Community Dent Health* 2000; 18: 72–78.
- Freeman R, Breistein B, McQueen A, Stewart M. The dental health status of five-year-old children in North and West Belfast. *Community Dent Health* 1997; 14: 253–257.
- Garcia-Closas R, Garcia-Closas M, Serra-Majem L. A cross sectional study of dental caries, intake of confectionary and foods rich in starch and sugars, and salivary counts of *Streptococcus mutans* in children in Spain. *Am J Clin Nutr* 1997; 66: 1257–1263.
- Grindeford M, Dahloff G, Nilsson B, Modeer T. Prediction of dental caries development in 1-year-old children. *Caries Res* 1995; 29: 343–348.
- Grindeford M, Dahloff G, Nilsson B, Modeer T. Stepwise prediction of dental caries in children up to 3.5 years of age. *Caries Res* 1996; 30: 256–266.
- Holbrook WP, Kristinson MJ, Gunnarsdottir S, Briem B. Caries prevalence, streptococcus mutans and sugar intake among 4-year-old children in Iceland. *Community Dent Oral Epidemiol* 1989; 17: 292–295.
- Holbrook WP, de Soet JJ, de Graff J. Prediction of dental caries in pre-school children. *Caries Res* 1993; 27: 424–430.
- Holt RD. Foods and drinks at four daily intervals in a group of young children. *Br Dent J* 1991; 170: 137–143.
- Ismail AI. Food cariogenicity in Americans aged 9 to 29 years assessed in a national cross-sectional survey. 1871–74. *J Dent Res* 1986; 65: 1435–1440.
- Karjalainen S, Soderling E, Sewon L, Lapinleimu H, Simell O. A prospective study on sucrose consumption, visible plaque and caries in children from 3 to 6 years of age. *Community Dent Oral Epidemiol* 2001; 29: 136–142.
- Kleemola-Kujala E, Rasanen L. Dietary pattern of Finnish children with low and high caries experience. *Community Dent Oral Epidemiol* 1979; 7: 199–205.
- Mazengo CM, Tenovuo J, Hausen H. Dental caries in relation to diet, saliva and cariogenic microorganisms in Tanzanians of

- selected age groups. *Community Dent Oral Epidemiol* 1996; **24**: 169–174.
- McMahon J, Parnell WR, Spears GFS. Diet and dental caries in preschool children. *Eur J Clin Nutr* 1993; **47**: 794–802.
- Petti S, Panfili P, Tarsitani G, Simonetti D'Arca A. Oral hygiene, sucrose consumption and dental caries prevalence in adolescent systemic fluoride non-users. *Community Dent Oral Epidemiol* 1997; **25**: 334–336.
- Rodrigues CS, Sheiham A. The relationship between dietary guidelines, sugar intake and caries in primary teeth in low income Brazilian 3-year-olds: a longitudinal study. *Int J Paediatr Dent* 2000; **10**: 47–55.
- Rugg-Gunn A, Hackett AF, Appleton D, Jenkins GN, Eastoe J. Relationship between dietary habits and caries increment assessed over two years in 405 English adolescent school children. *Arch Oral Biol* 1984; **29**: 983–992.
- Sampaio FC, Nazmul Hossain ANM, von der Fehr FR, Arneberg P. Dental caries and sugar intake of children from rural areas with different water fluoride levels in Paraiba, Brazil. *Community Dent Oral Epidemiol* 2000; **28**: 307–313.
- Serra-Majem L, Garcia-Closas R, Ramon J, Manau C, Cuenca E, Krasse B. Dietary habits and dental caries in a population of Spanish school children with low levels of caries experience. *Caries Res* 1993; **27**: 488–494.
- Sgan-Cohen H, Lipsky R, Behar R. Caries, diet, dental knowledge and socio-economic variables in population of 15-year-old Israeli school children. *Community Dent Oral Epidemiol* 1984; **12**: 332–336.
- Stecksén-Blicks C, Holm A. Between-meal eating, toothbrushing frequency and dental caries in 4-year-old children in the North of Sweden. *Int J Paediatr Dent* 1985; **5**: 67–72.
- Stecksén-Blicks C, Holm AK, Mayanagi H. Dental caries in Swedish 4-year-old children. Changes between 1967 and 1987. *Swed Dent J* 1989; **13**: 39–44.
- Sundin B, Birkhed D, Granath L. Is there not a strong relationship nowadays between caries and consumption of sweets? *Swed Dent J* 1983; **7**: 103–108.
- Sundin B, Granath L, Birkhed D. Variation of posterior approximal caries incidence with consumption of sweets with regard to other caries-related factors in 15-18-year-olds. *Community Dent Oral Epidemiol* 1992; **20**: 76–80.
- Clancy KL, Bibby BG, Goldberg HJV, Ripa LW, Barenie J. Snack food intake of adolescents and caries development. *J Dent Res* 1977; **56**: 568–573.
- Cleaton-Jones P, Richardson BD, Sreebny LM, Fatti P, Walker AR. The relationship between the intake frequency and the total consumption of sucrose among four South African ethnic groups. *J Dent Child* 1987; **54**: 251–254.
- Duany LF, Zinner DD, Jablon JM. Epidemiological studies of caries-free and caries-active students: II. Diet, dental plaque and oral hygiene. *J Dent Res* 1972; **51**: 727–733.
- Garn SM, Cole PE, Solomon MA, Schaefer AE. Relationships between sugar-foods and the DMFT in 1968–1970. *Ecol Food Nutr* 1979; **9**: 135–138.
- Gibson S, Williams S. Dental caries in pre-school children: associations with social class, tooth brushing habit and consumption of sugars and sugar-containing foods. Further analysis of data from the National Diet and Nutrition Survey of children aged 1.5–4.5 years. *Caries Res* 1999; **33**: 101–113.
- Glass R, Fleisch S. Diet and dental caries: dental caries incidence and the consumption of ready-to-eat cereals. *J Am Dent Assoc* 1974; **88**: 807–813.
- Gordon Y, Reddy J. Prevalence of dental caries, patterns of sugar consumption and oral hygiene practices in infancy in S. Africa. *Community Dent Oral Epidemiol* 1985; **13**: 310–314.
- Granath L, Rootzén H, Liljgren E, Holst K, Köhler L. Variation in caries prevalence related to combinations of dietary and oral hygiene habits and chewing fluoride tablets in 4-year-old children. *Caries Res* 1978; **12**: 83–92.
- Grobler SR. The effect of a high consumption of citrus fruit and a mixture of other fruits on dental caries in man. *Clin Prev Dent* 1991; **13**: 13–17.
- Grythen J, Rossow I, Holst D, Steele L. Longitudinal study of dental health behaviours and other caries predictors in early childhood. *Community Dent Oral Epidemiol* 1988; **16**: 356–359.
- Gustaffson B, Quensel C-E, Swenander Lanke L, Lundqvist C, Grahnen H, Bonow B, Krasse B. The Vipeholm dental caries study. The effect of different levels of carbohydrate intake on caries activity in 436 individuals observed for five years. *Acta Odontol Scand* 1954; **11**: 232–264.
- Hankin JH, Chung CS, Kau MCW. Genetic and epidemiological studies in Hawaii's schoolchildren: dietary patterns and caries prevalence. *J Dent Res* 1973; **52**: 1079–1086.
- Hargreaves JA. Changes in diet and dental health of children living in the Scottish island of Lewis. *Caries Res* 1972; **6**: 355–376.
- Hausen H, Heinonen OP, Paunio I. Modification of occurrence of caries in children by toothbrushing and sugar exposure in fluoridated and non-fluoridated areas. *Community Dent Oral Epidemiol* 1981; **9**: 103–107.
- Holbrook WP, Árnadóttir IB, Takazoe I, Birkhed D, Frostell G. Longitudinal study of caries, cariogenic bacteria and diet in children just before and just after starting school. *Eur J Oral Sci* 1995; **103**: 42–45.
- Hollund U. Relationship between diet-related behaviour and caries in a group of 14-year-old Danish children. *Community Dent Oral Epidemiol* 1987; **15**: 184–187.
- Jamel HA, Sheiham A, Watt RG, Cowell CR. Sweet preference, consumption of sweet tea and dental caries: studies in urban and rural Iraqi populations. *Int Dent J* 1997; **47**: 213–217.
- Johnsen D, Pappas I, Cannon D, Goodman S. Social factors and diet diaries of caries-free and high-caries 2- to 7-year-olds presenting for dental care in West Virginia. *Pediatr Dent* 1980; **2**: 279–286.
- Kalsbeek H, Verrips GH. Consumption of sweet snacks and caries experience of primary school children. *Caries Res* 1994; **28**: 477–483.

- Kerosuo H, Honkala E. Caries experience in the primary dentition of Tanzanian and Finnish 3-7-year-old children. *Community Dent Oral Epidemiol* 1991; **19**: 272-276.
- Kuusela S, Honkala E, Rimpela S. How does the use of different sugar products predict caries in 18-year-old Finns? *J Dent Child* 1997; **64**: 123-127.
- Kuusela ST, Kannas L, ynjala J, Honkala E, Tudor-Smith C. Frequent use of sugar products by school children in 20 European countries, Israel and Canada in 1993/1994. *Int Dent J* 1999; **49**: 105-114.
- Lachapelle D, Couture C, Brodeur J, Sevigny J. The efficacy of Nutritional quality and frequency of consumption of sugary foods on dental caries increment. *Can J Public Health* 1990; **81**: 370-375.
- Larsson B, Johansson I, Erickson T. The prevalence of caries in adolescents in relation to diet. *Community Dent Oral Epidemiol* 1992; **20**: 133-137.
- Levine RS, Nugent ZJ, Rudolf MC, Sahora P. Dietary patterns, toothbrushing habits and caries experience of schoolchildren in West Yorkshire, England. *Community Dent Health* 2007; **24**: 82-87.
- Marques A, Messer L. Nutrient intake and dental caries in the primary dentition. *Pediatr Dent* 1992; **14**: 314-325.
- Marshall TA, Broffitt B, Eichenberger-Gilmore J, Warren JJ, Cunningham MA, Levy SM. The roles of meal, snack and daily total food and beverage exposures on caries experience in young children. *J Public Health Dent* 2005; **65**: 166-173.
- Martinsson T. Socio-economic investigation of school children with high and low caries frequency III. A dietary study based on information given by the children. *Odontol Revy* 1972; **23**: 93-113.
- Masalin KE, Murtomaa HT, Sipilä KPJ. Dental caries risk in relation to dietary habits and dental services in two industrial populations. *J Public Health Dent* 1994; **54**: 160-166.
- Neiderud J, Birkhed D, Neiderud A. Dental health and dietary habits in Greek and immigrant children in southern Sweden compared with Swedish and rural Greek children. *Swed Dent J* 1991; **15**: 187-196.
- Normark S. Social indicators of dental caries among Sierra Leonean school children. *Scand J Dent Res* 1993; **101**: 121-129.
- Petridou E, Athanassouli T, Panagopoulos H, Revinthi K. Socio-demographic and dietary factors in relation to dental health among Greek adolescents. *Community Dent Oral Epidemiol* 1996; **24**: 307-311.
- Reekola M. Approximal caries development during 2-year total substitution of dietary sucrose with Xylitol. *Caries Res* 1987; **21**: 87-94.
- Retief D, Cleaton-Jones P, Walker A. Dental caries and sugar intake in South African pupils of 16 to 17 years in four ethnic groups. *Br Dent J* 1975; **138**: 463-469.
- Richardson A, Boyd M, Conry R. A correlation study of diet, oral hygiene and dental caries in 457 Canadian children. *Community Dent Oral Epidemiol* 1977; **5**: 227-230.
- Richardson BD, Cleaton-Jones P, McInnes PM, Rantsho JM, Pieters L. Total sucrose intake and dental caries in Black and White South African children of 1-6 years. Part II: Dental caries and sucrose intake. *J Dent Assoc S Afr* 1978; **33**: 539-544.
- Sahoo P, Tewari A, Chawla H, Sachdev V. Interrelationship between sugar and dental caries - a study in child population of Orissa. *J Indian Soc Pedod Prev Dent* 1992; **10**: 37-44.
- Sampaio FC, Nazmul Hossain ANM, von der Fehr FR, Arneberg P. Dental caries and sugar intake of children from rural areas with different water fluoride levels in Paraiba, Brazil. *Community Dent Oral Epidemiol* 2000; **28**: 307-313.
- Sgan-Cohen H, Salinger E. Dental caries and sugar intake, during and between meals, in children of an Israeli Kibbutz. *Community Dent Oral Epidemiol* 1982; **10**: 52-53.
- Sgan-Cohen H, Lipsky R, Behar R. Caries, diet, dental knowledge and socio-economic variables in population of 15-year-old Israeli school children. *Community Dent Oral Epidemiol* 1984; **12**: 332-336.
- Sgan-Cohen H, Katznelson J. Diet and dental caries in 4 to 8 year old children on a kibbutz. *Isr J Dent Sci* 1988; **2**: 109-113.
- Silver D. A longitudinal study of infant feeding practice, diet and caries, related to social class in children aged 3 and 8-10 years. *Br Dent J* 1987; **163**: 296-300.
- Sreebny L. Sugar availability, sugar consumption and dental caries. *Community Dent Oral Epidemiol* 1982; **10**: 1-7.
- Stecksen-Blicks C, Borssen E. Dental caries, sugar-eating habits and toothbrushing in groups of 4-year-old children 1967-1997 in the city of Umea, Sweden. *Caries Res* 1999; **33**: 409-414.
- Steyn N, Albertse E, van Wyk Kotze T, van Eck C, van Eck M. Sucrose consumption and dental caries in twelve-year-old children of all ethnic groups residing in Cape Town. *J Dent Assoc S Afr* 1987; **42**: 43-49.
- Sundin B. Caries and consumption of sweets in 15- and 18-year-olds interviewed with visualisation. *Scand J Dent Res* 1990; **98**: 96-101.
- Sundin B, Granath L. Sweets and other sugary foods tend to be the primary etiological factors in dental caries. *Scand J Dent Res* 1992; **100**: 137-139.
- Szpunar S, Ekland S, Burt B. Sugar consumption and caries risk in school children with low caries experience. *Community Dent Oral Epidemiol* 1995; **23**: 142-146.
- Takahashi K. Statistical study on caries incidence in the first molar in relation to the amount of sugar consumption. *Bull Tokyo Dent Coll* 1961; **2**: 44-57.
- Takuechi M. Epidemiological study on relationship between dental caries incidence and sugar consumption. *Bull Tokyo Dent Coll* 1960; **1**: 58-70.
- Tubert-Jeannin S, Lardon J-P, Pham E, Martin J-L. Factors effecting caries experience in French adolescents. *Community Dent Oral Epidemiol* 1994; **22**: 30-35.
- Walker A. Sugar intake and dental caries in pupils in four South African ethnic groups. *S Afr Med J* 1975; **49**: 616-619.
- Walker A, Dison E, Walker B, Friedlander I, Aucamp V. Dental caries in South African Black and White high school pupils in relation to sugar intake and snack habits. *Community Dent Oral Epidemiol* 1980; **9**: 37-43.
- Wendt LK, Birkhed D. Dietary habits related to caries development and immigrant status in infants and toddlers living in Sweden. *Acta Odontol Scand* 1995; **53**: 339-344.
- Wilson RF, Ashley FP. Identification of caries risk in school children: salivary buffering capacity and bacterial counts, sugar intake and caries experience as predictors of 2-year and 3-year caries increment. *Br Dent J* 1989; **166**: 99-102.
- Yabao RN, Duante CA, Velandria FV, Lucas M, Kassu A, Nakamori M, Yamamoto S. Prevalence of dental caries and sugar consumption among 6-12 y-old schoolchildren in La Trinidad, Benguet, Philippines. *Eur J Clin Nutr* 2005; **59**: 1429-1438.
- Zita A, McDonald R, Andrews A. Dietary habits and the dental caries experience in 200 children. *J Dent Res* 1959; **38**: 860-865.

Overview

Summary and general conclusions/outcomes on the role and fate of sugars in human nutrition and health

L. Arola¹, M. L. Bonet², N. Delzenne³, M. S. Duggal⁴, C. Gómez-Candela⁵, A. Huyghebaert⁶, M. Laville⁷, P. Lingström⁸, B. Livingstone⁹, A. Palou², C. Picó², T. Sanders¹⁰, G. Schaafsma¹¹, M. van Baak¹², C. van Loveren¹³ and E. M. van Schothorst¹⁴

¹Department of Biochemistry and Biotechnology, University Rovira i Virgili, Tarragona, Spain; ²Laboratory of Molecular Biology, Nutrition and Biotechnology, Universitat de les Illes Balears and CIBER Fisiopatologia de la Obesidad y Nutrición, Palma de Mallorca, Spain; ³Unit of Pharmacokinetics, Metabolism, Nutrition and Toxicology, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; ⁴Department of Paediatric Dentistry, Leeds Dental Institute, Leeds, UK; ⁵Nutrition Department, Hospital La Paz, Madrid, Spain; ⁶Faculty Bioscience Engineering, Ghent University, Ghent, Belgium; ⁷Centre de Recherche en Nutrition Humaine Rhône-Alpes (CRNH-RA), Hôpital Edouard Herriot, Lyon, France; ⁸Department of Cariology, Institute of Odontology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; ⁹Northern Ireland Centre for Food and Health, University of Ulster, Londonderry, UK; ¹⁰Nutritional Science Division, King's College London, London, UK; ¹¹Research group on sports, nutrition and lifestyle, HAN University, Nijmegen, The Netherlands; ¹²NUTRIM, Department of Human Biology, Maastricht University, Maastricht, The Netherlands; ¹³Department of Cariology Endodontology Pedodontology, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, the Netherlands; ¹⁴Human and Animal Physiology, Wageningen University, Wageningen, The Netherlands

Received 30 October 2008; accepted 18 November 2008

Address for correspondence: Professor Andreu Palou, Laboratori de Biologia Molecular, Nutrició i Biotecnologia, Departament de Biologia Fonamental i Ciències de la Salut, Universitat de les Illes Balears, Crta. Valldemossa Km 7.5, 07122 Palma de Mallorca, Spain. E-mail: andreu.palou@uib.es

A scientific expert workshop was organized to review the controversial aspects of the role of sugars in relation to human health (see paper by Palou *et al.* in this issue (1)). Particular attention was paid to the quality of the scientific evidence and to identifying areas where further research is required. Consideration was given to the following topics covering potential effects of dietary sugars on (i) overweight and obesity (see paper by van Baak and Astrup in this issue (2)); (ii) insulin resistance and diabetes (see paper by Laville and Nazare in this issue (3)); (iii) dental caries (see paper by Anderson *et al.* in this issue (4)) and (iv) micronutrient dilution (see paper by Livingstone and Rennie in this issue (5)).

The term 'sugars' generally refers to monosaccharides and disaccharides present from whatever source in a food excluding polyols (sugar alcohols), and was also the definition adopted for the purposes of this exercise.

The working method adopted was to discuss review papers prepared prior to the meeting and to assess the evidence according to guidelines recommended by the World Health Organization (WHO) in order to establish relationships between food and health. According to the WHO expert group, there is convincing evidence when consistent associations between exposure and disease have been found in epidemiological studies; when the relevance is estimated through the availability of a substantial number of studies – including prospective observational studies and, where relevant, randomized controlled trials of sufficient size, duration and quality – showing consistent effects; and when the associations have biological plausibility (6).

Sugars in overweight and obesity

The main conclusions on this topic are:

1. Epidemiological studies and randomized controlled trials (RCT) show fairly consistent inverse associations between the carbohydrate and sugar content of the diet, and body weight and adiposity. The evidence can be considered probable when fat in the diet is replaced by carbohydrates – either in the form of sugars or complex carbohydrates; a small weight loss occurs owing to a decreased energy intake.

2. There is insufficient evidence that an exchange of sugar for non-sugar carbohydrates in the context of a reduced-fat *ad libitum* diet or energy-restricted diet results in greater weight reduction. Additional RCT, strictly controlling macronutrient ratios and fiber content, are necessary to definitively assess the effect of exchange of sugars for non-sugar carbohydrates on body-weight control.

3. There is concern regarding a possible relationship between a high consumption of sugar-sweetened beverages (SSB) (including juices and nectars) and obesity, especially in children and young adults. This is suggested from cross-

sectional data as well as cohort studies, showing that there is a possible association between SSB consumption and excess body weight. One underlying hypothesis is that the sugar calories in liquids have little effect on satiety and therefore easily lead to over-consumption although SSB consumption may also represent a marker of a particular lifestyle.

4. A limited number of RCT have compared changes in body weight when SSB are replaced with artificially sweetened drinks, but the results are equivocal. More RCT of sufficient size and duration would be required in this area to support the data from epidemiological studies.

5. There is a clear need for more RCT of sufficient size and duration to compare effects of liquid vs. solid sugars on satiety, energy intake, compensation responses and other functions related with body-weight control.

6. There is currently no evidence that an *ad libitum* diet with a low glycaemic index causes more weight loss than a diet with a high glycaemic index when total carbohydrate intake is not different. There is some limited evidence from randomized controlled trials that *ad libitum* and moderately energy-restricted diets with a low glycaemic load are associated with modest body-weight loss compared with diets with a high glycaemic load. Whether or not there is a specific effect of glycaemic load, or of total amount of carbohydrate, needs to be elucidated.

Sugars in insulin resistance and diabetes

It was judged that there is insufficient evidence to demonstrate an association between dietary intake of sugars and the development of insulin resistance and type 2 diabetes from human studies. It was noted that current dietary recommendations for the management of type 1 and type 2 diabetes do not specify restriction of sugar intake but focus on weight management and the pattern of total carbohydrate intake throughout the day to avoid large fluctuations in blood glucose levels.

Impact of many dietary and lifestyle factors such as physical activity, excessive calorie intake and weight gain has to be taken into account. Obesity and low physical activity are causally related to the development of insulin resistance and its progression towards type 2 diabetes. There is convincing evidence from RCT that weight loss and physical activity are beneficial in improving insulin sensitivity and preventing type 2 diabetes.

There is uncertainty about the long-term effects of fructose on insulin sensitivity and associated disorders compared with other sugars. The evidence is insufficient to support substitution of sucrose by fructose. Consideration should be given to assessing the potential impact on health of replacing sugar by other food components.

More studies are needed in order to determine the impact of strict restriction of simple carbohydrates intake on

glucose and insulin metabolism, and weight reduction in order to make dietary recommendations to limit the risk of diabetes.

Sugars in dental caries

Although it is generally agreed that fermentable carbohydrates are required for causation of dental caries, there is still ongoing debate of the exact role of dietary sugars in the modern society. This interrelation is influenced by a large number of factors of which an important one is the widespread use of fluoridated toothpaste. This has weakened the relationship and has reduced the impact of sugars on dental caries on a population level.

A systematic review of the literature was conducted to assess the relationship between quantity and pattern of sucrose intake and dental caries in children and young adults. The analysis showed that there is no clear relationship of quantity of sugar used to dental caries, while there is evidence for a relationship between frequency of sugar consumption and dental caries.

Future research should focus on the role of sugars in relation to dental caries taking into account lifestyle factors and the way sugar is consumed within the diet in the modern society and in different age groups. The interaction of diet with preventive methods, in particular fluoride, warrants further studies. Although we accept that given the length of time for caries to manifest and the complexity of the disease it is difficult to conduct RCT, it is important that well-designed studies are undertaken.

Sugars and micronutrient dilution

Debates about the role of added sugars in promoting micronutrient dilution have been longstanding. The overall conclusion to emerge from the existing evidence, based mainly on cross-sectional observational studies, is that associations between reported intakes of added sugars and intakes of micronutrients are inconsistent and often non linear, both across and within age groups, and between the genders. In the context of intake of a diet with appropriate energy it appears that the consumption of a wide range of added sugar is compatible with an adequate micronutrient intake; if a nutrient displacement effect does exist, a high consumption of added sugar does not necessarily compromise overall micronutrient intakes and similarly, consuming less added sugar is no guarantee that micronutrient intakes will be optimized.

The observed associations between added sugars and micronutrient intake have been heavily contingent on both the definition of sugars chosen and the analytical approach used for adjusting for differences in reported energy intake. These issues have been further compounded by misreporting of food intake of unknown direction and magnitude

and the cut-offs used to determine 'inadequate' micronutrient intakes which vary over time and between studies and countries.

Recommendations for future research

Most information about the relationship between dietary carbohydrates/sugars and health comes from observational epidemiological studies that cannot prove causality and in which it is conceivable that, at least in part, carbohydrate in diets simply act as a marker of some other factors. There is in the field of RCT a clear need for studies of sufficient size and duration to contrast the conclusions of epidemiological studies.

The evaluation of the effects (risks and benefits) of food on health is usually limited to only one potential target (or a few of them) for reasons of simplicity, but ideally all effects should be considered. Future studies addressing the integral role of sugars on human health should consider altogether the different targets (metabolic-obesity-insulin, energy/nutrient balance, dental caries) in long-term circumstances. Moreover, because specific carbohydrates, as other dietary chemicals, can entail both health benefits and risks, there is the need to obtain more complete biomarker profiles, rather than focusing on individual biomarkers or end-points. Approaches involving the use of post-genomic technologies (nutrigenomics) may be particularly useful in this context.

Specific effects of carbohydrates on regulatory circuitries controlling physiological responses and gene expression are progressively unveiled and need to be understood at the molecular level. The elucidation of the mechanisms of action might initially be performed using homogeneous animal models and subsequently be translated to, and analysed, in human situation. For instance, the increasing incidence of obesity and related diseases worldwide is nowadays enhancing an intensive study of the role of carbohydrates as potential regulators of energy balance (e.g. by regulating appetite and/or energy expenditure) or other processes specifically involved in obesity development, where specific cause-effects and mechanisms behind can be identified for defined chemical species and combinations.

All in all, it is recognized that new studies are required to help setting up more precise figures for sugar and carbohydrate intake recommendations.

Conflict of Interest Statement

T. Sanders has acted as a paid consultant to aspartame advisory service to Beneo T in respect of artificial sweeteners and as an advisor to the Breakfast Cereals Information Services; he has chaired Cadbury PLC Global Nutrition Advisory Board and has served as a member of the Scientific Advisory Committee on the

Malaysian Palm Oil Board and of the Global Dairy Platform. B. Livingstone has received a grant from Unilever; M. van Baak is recipient of research grants and honoraria as speaker from a number of Dutch and international companies and has no conflict of interest related to sugar.

M. Laville has received speaker fees from Benjamin Delessert Institute and from the European Scientific Workshop on Sugars. L. Arola, M.L. Bonet, N. Delzenne, C. Gómez-Candela, M.S. Duggal, A. Huyghebaert, A. Palou, C. Picó, G. Schaafsma, P. Lingström, C. van Loveren and E.M. van Schothorst have no conflict of interest to declare.

Acknowledgements

The funding for the organization of the scientific workshop was provided by an unrestricted grant from the Asociación General de Fabricantes de Azúcar de España (AGFAE) and the Comité Européen des Fabricants de Sucre (CEFS).

Reference

1. Palou A, Bonet ML, Picó C. On the role and fate of sugars in human nutrition and health. Introduction. *Obesity Reviews* 2009; 10(Suppl. 1): 1–8.
2. van Baak MA, Astrup A. Consumption of sugars and body weight. *Obesity Reviews* 2009; 10(Suppl. 1): 9–23.
3. Laville M, Nazare J.-A. Diabetes, insulin resistance and sugars. *Obesity Reviews* 2009; 10(Suppl. 1): 24–33.
4. Anderson CA, Curzon MEJ, Van Loveren C, Tatsi C, Duggal MS. Sucrose and dental caries: a review of the evidence. *Obesity Reviews* 2009; 10(Suppl. 1): 41–54.
5. Livingstone MBE, Rennie KL. Added sugars and micronutrient dilution. *Obesity Reviews* 2009; 10(Suppl. 1): 34–40.
6. WHO. Diet, nutrition, and the prevention of chronic diseases. Report of a Joint WHO/FAP Expert Consultation. WHO Technical Report Series No. 916, World Health Organization, Geneva, Switzerland, 2003.